2024 Breast Cancer Congress
with Updates from the 2023 SABCS

Friday, February 2, 2024
11:45 AM – 12:10 PM CST

Updates to Radiation Therapy for Invasive Breast Cancer and DCIS with SABCS Updates

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Who Can We Observe After Breast Conserving Surgery (BCS)?

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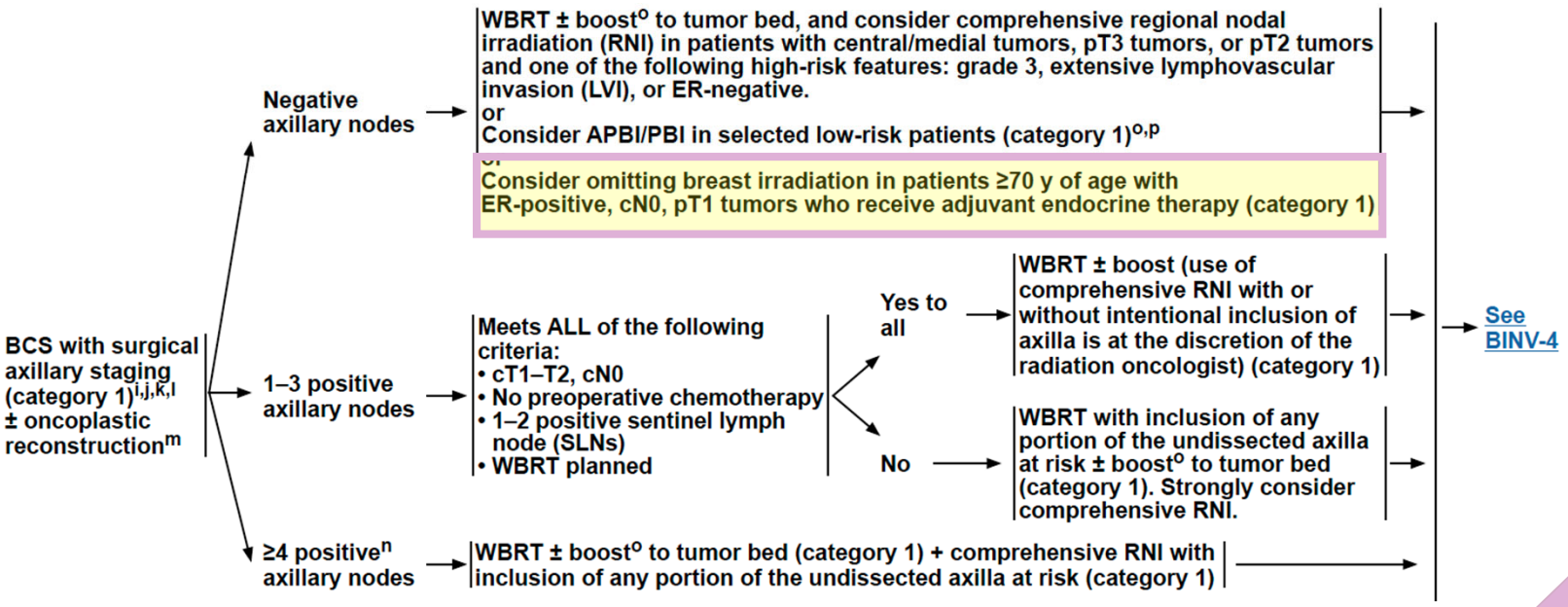
NCCN Guidelines Version 5.2023
Invasive Breast Cancer

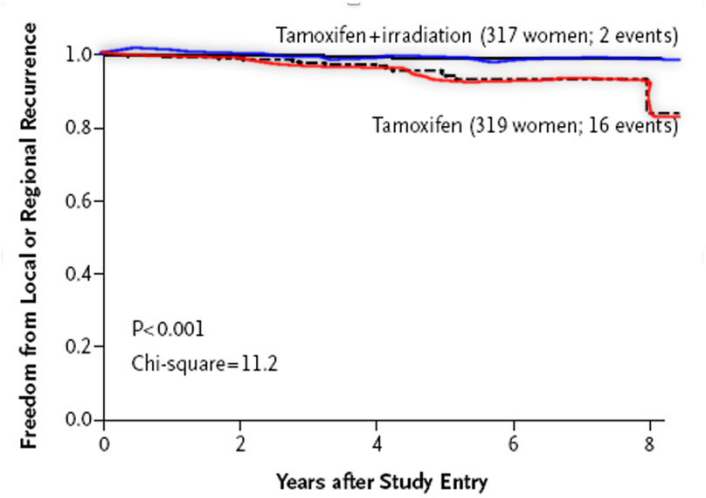
LOCOREGIONAL TREATMENT OF cT1–3, cN0 or cN+, M0 DISEASE:[a]
BREAST-CONSERVING SURGERY (BCS) FOLLOWED BY RT

RT AFTER COMPLETION OF BCS AND AXILLARY STAGING

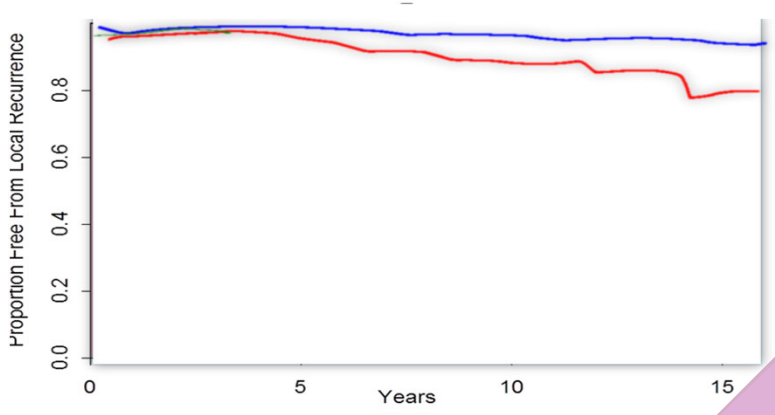


CALGB 9343 Long Term Outcomes

12 yr Outcomes	Tam+RT	Tam	P value
Ax Rec	1%	0%	NS
Mastectomy Rate	2%	4%	NS
Distant Mets	5%	5%	NS
10 year BCSS	98%	97%	NS



Local Relapse	5 yr	8 yr	10yr
Tam + RT	1%	1%	2%
Tam	4%	7%	10%
P value	<0.001	<0.001	0.001



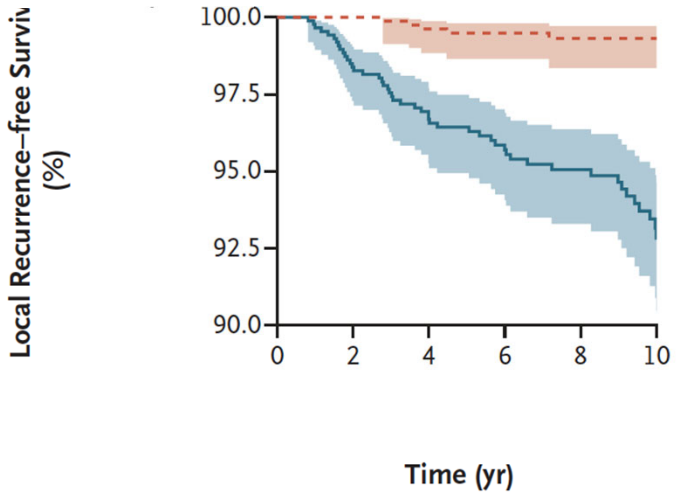
Hughes et. al. NEJM 2004, JCO 2013

PRIME II TRIAL: 10 Year Outcomes

N=1370
≥65 yrs age
<3cm
pN0*
*axilla surgically assessed

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 FEBRUARY 16, 2023 VOL. 388 NO. 7

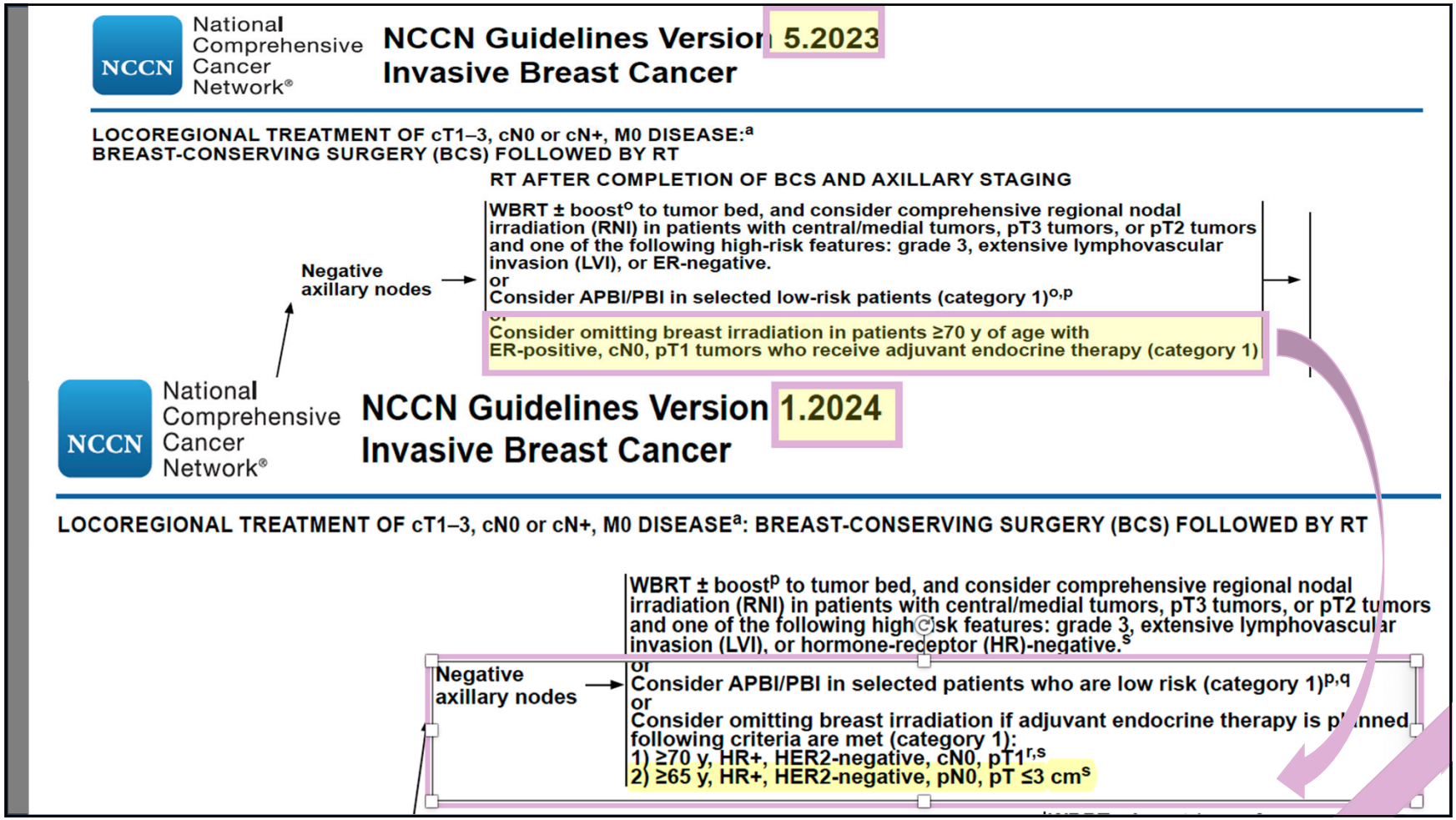
Breast-Conserving Surgery with or without Irradiation in Early Breast Cancer



Patient Characteristics	
Median age:	70 yrs
Tumors <2 cm:	90%
Grade I or II:	90%

Local Relapse	5 yr	10yr
Tam + RT	1.3	0.9%
Tam	4%	9.5%
P value	0.0002	<0.001

Kunkler et al, Feb 2023 , NEJM



Invasive Breast Cancer

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Invasive Breast Cancer

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LOCOREGIONAL TREATMENT OF cT1–3, cN0 or cN+, M0 DISEASE[a]: BREAST-CONSERVING SURGERY (BCS) FOLLOWED BY RT

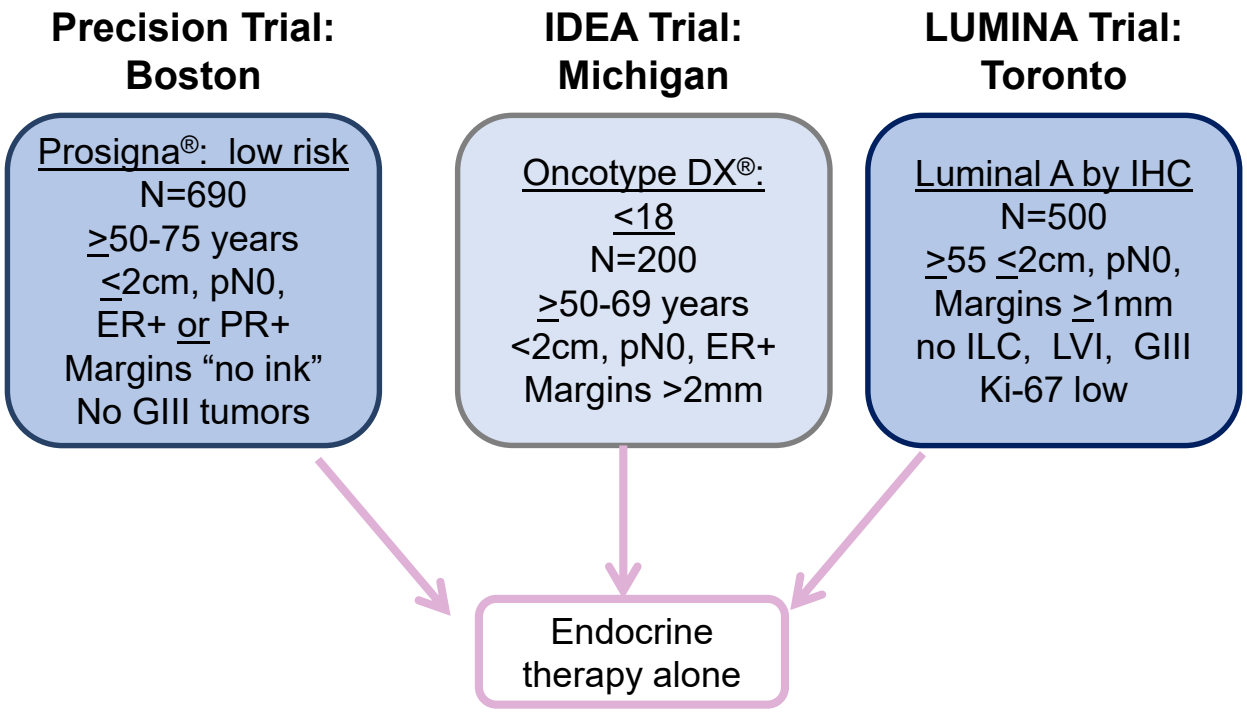
BCS[j] with surgical axillary staging (category 1)[i,k,l,m] ± oncoplastic reconstruction[n]

→ Negative axillary nodes

Consider omitting breast irradiation if adjuvant endocrine therapy is planned following criteria are met (category 1):
1) ≥70 y, HR+, HER2-negative, cN0, pT1[r]
2) ≥65 y, HR+, HER2-negative, pN0, pT ≤3 cm[s]

Choosing Wisely®
An initiative of the ABIM Foundation

Omission of RT after BCS: Prospective, Single-Arm Trials Using Tumor Biology



5 Year Results: LuminA TRIAL

Single Arm Prospective Study

N=500

Age ≥55
≤2cm, N0,
ER>1,
PR>20%,
HER-2 neu 0

IHC Central Lab
Ki-67 Tested

If Ki-67<13.25%

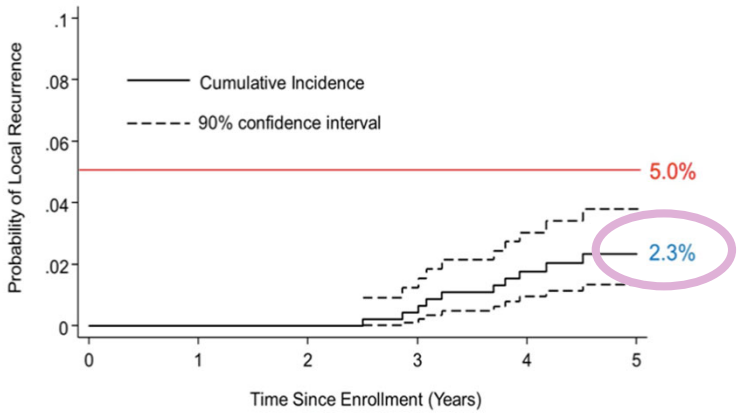
Enrolled

Received ET
Alone

If Ki-67<13.25%

Not Enrolled

Local Recurrence



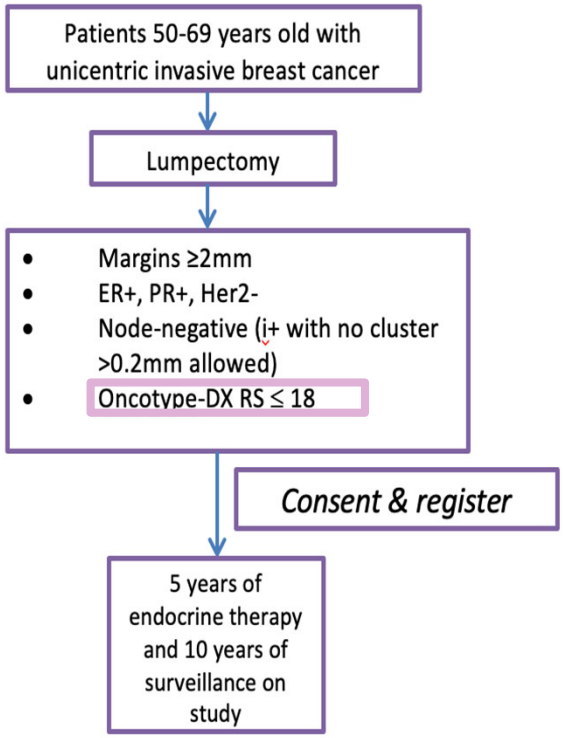
Patient Characteristics	
Mean age	67 yrs
Mean tumor size	1.1 cm
Grade I or Grade II	100%
Tamoxifen vs. AI	41% vs. 59%

5 yr Outcomes	
Median Follow up	HT
Local Relapse	2.3 %

Whelan T, et al ASCO 2022, NEJM 2023

SABCS 2023: 5 Year Results: IDEA Trial

Single Arm Prospective Study



N=200 enrolled

RESULTS:

Median f/u: 5.2 years

Pt Characteristics:

Mean age: 62 years

Mean tumor size: 10 mm

Mean 21-gene RS: 11

MRI: 33%

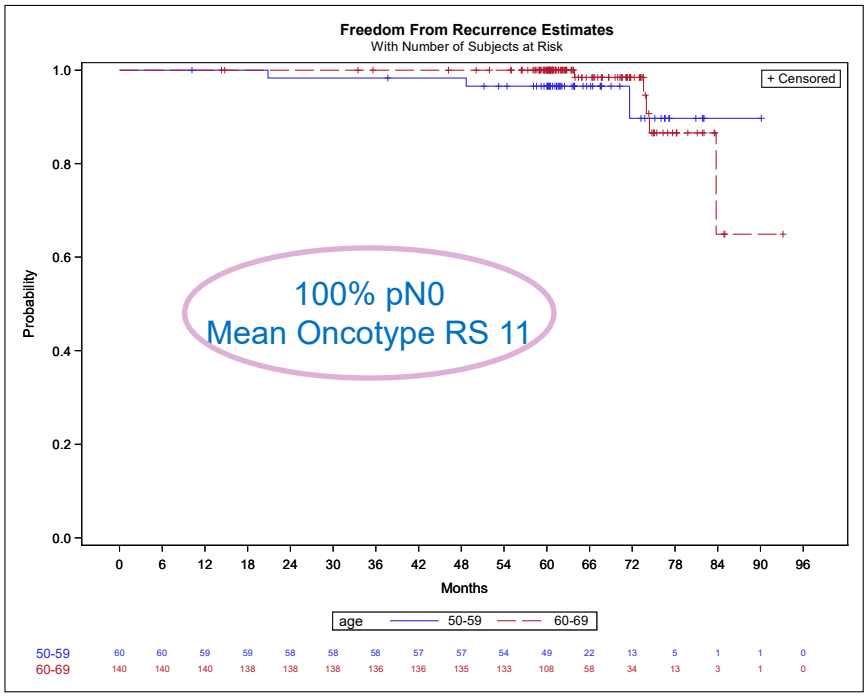
ER+/PR+/HER2-: 100%

GI or GII: 97%

No LVSI: 86%

Jagsi, SABCS 2023

5 Year Results: IDEA Trial
Single Arm Prospective Study



- **Crude rates of IBE:**
  - 3.3% (2/60) for patients aged 50-59
  - 3.6% (5/140) for patients aged 60-69
- **Crude rates of overall recurrence:**
  - 5.0% (3/60) for patients aged 50-59
  - 3.6% (5/140) for patients aged 60-69

Jagsi, SABCS 2023

Current Trials Using Biologic Criteria for RT Omission
(Accruing or Active Follow-up)

	Lumina	Idea	Precision	Primetime	Europa	Expert	Natural	Debra
	Single Arm Prospective				Randomized Prospective			
Years	2013-2017	2013-2017	2016-present	2017-2022	2021-present	2017-present	2018-present	2021-present
Accrual Goal	501	501	672	2400	926	1167	926	1670
Age	≥ 55	≥ 55	≥ 50 ≤ 75	≥ 60	≥ 70	≥ 50	≥ 60	≥ 50 ≤ 70
T Stage	pT1	pT1	pT1	pT1	pT1	pT1	pT1	pT1
N Stage	pN0	pN0	pN0, pN0(IHC+)	pN0	cN0, pN0, pN0(IHC+)	pN0, pN0(IHC+)	pN0	pN0
Grade	1-2	1-2	1-2	1-2	Any if ≤1 cm 1-2 if >1 cm	1-2	1-2	Any
Biologic criteria	IHC ER≥1%PR>20 % HER2- Ki67≤13.25%	IHC ER≥1%PR>20 % HER2- Ki67≤13.25%	PAM-50 Low risk IHC ER/PR≥10% HER2-	IHC ER/PR+ HER2- IHC4+C Very low	IHC ER/PR≥10% HER2- Ki67≤20%	PAM-50 Luminal A ROR ≤60	IHC ER≥10% HER2-	Oncotype Score ≤18 IHC ER/PR≥1% HER2-
Trial Arms	ET	ET	ET	ET	ET vs. APBI	ET vs. ET + RT	ET vs. ET + APBI	ET vs. ET + RT

ET=Endocrine therapy; APBI=Accelerated partial breast radiation; RT=Radiation therapy

Who Should Currently Be Offered Omission of RT?

Eligible pts for omission of radiation:

- Those who are less likely to experience a 10+ year benefit
- Currently, only HR+, HER-2 negative; candidates for ET who meet:
  - PRIME II: ≥65-year-old, pathologically N0, T ≤3cm
  - CALGB 9343: ≥ 70 years old, clinically N0, T ≤2 cm

Willing to:

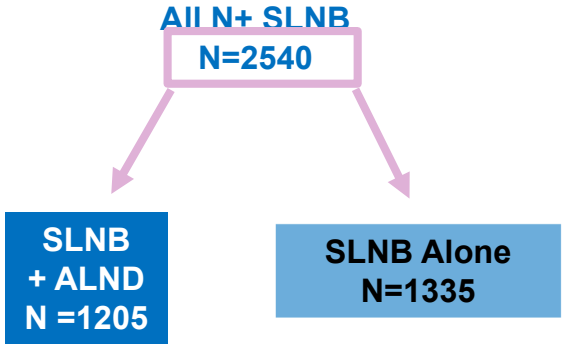
- Accept higher risk of LRR
- Commit to 5 years of ET
- Be compliant with regular screening/follow-up

AXILLARY MANAGEMENT

Evolution in NCCN Treatment Algorithms for Axillary (Ax) Management

- Rapid changes in axillary management for early-stage BC pts over last several years
- ACOSOG Z011: Shifted paradigm for omission of ALND for + SLN (up to 2+)
- Uncertainties regarding ACOSOG Z-011 trial:
  - Statistical power
  - Radiotherapy target volumes
  - Volume of disease in involved nodes minimal
- Under-represented subgroups
  - HR negative
  - Younger pts
  - Mastectomy
  - Larger tumors
- Since Z-011 publication, additional trials confirm low axillary recurrence risk, no difference in long-term outcomes with ALND or Ax-RT for ≤2 nodes+
- Have allowed for expansion of indications:
  - Sinodar
  - AMAROS
  - OTOASAR
- Ax management algorithms will continue to rapidly evolve with additional emerging data

SABCS 2023: Initial Results SEMONAC
Outcomes after SLNB+ BC without Completion ALND

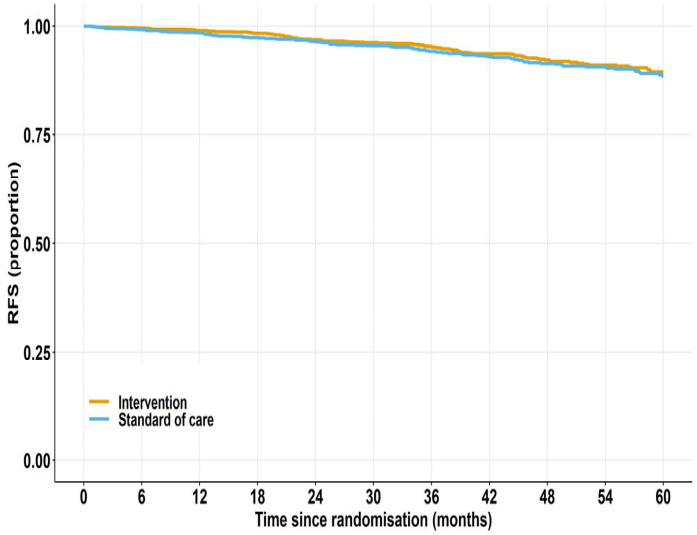


- Med F/u=47 months
- Med Age=61 years (range: 20-94) 60% were <65 years
- Median total nodes removed: 15 ALND vs. 2 SLNB alone
- 0.4% (10 pts) were male
- Median tumor size 2.0 cm
- 6% (147 pts) had T3
- 20% Lobular histology
- 85% had at least 1 macro-metastasis
- 36% Mastectomy
- 34% (870 pts) had extranodal extension
- 35%(403) had non-SLN mets on ALND
- 85% were ER+

Boniface J, et al. SABCS 2023

SABCS 2023: Initial Results SEMONAC Outcomes after SLNB+ BC +/- Completion ALND

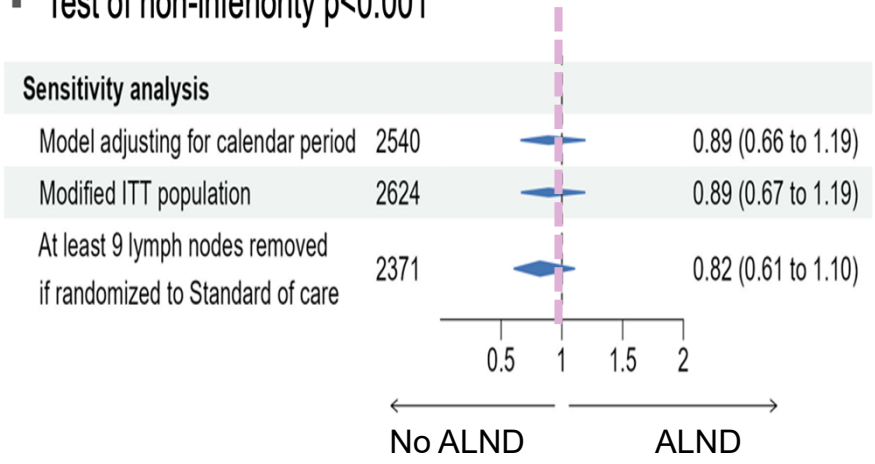
Recurrence-Free Survival



Boniface J, et al. SABCS 2023

Results: Non-inferiority

- Hazard ratio 0.89 (0.66-1.19)
- Test of non-inferiority p<0.001



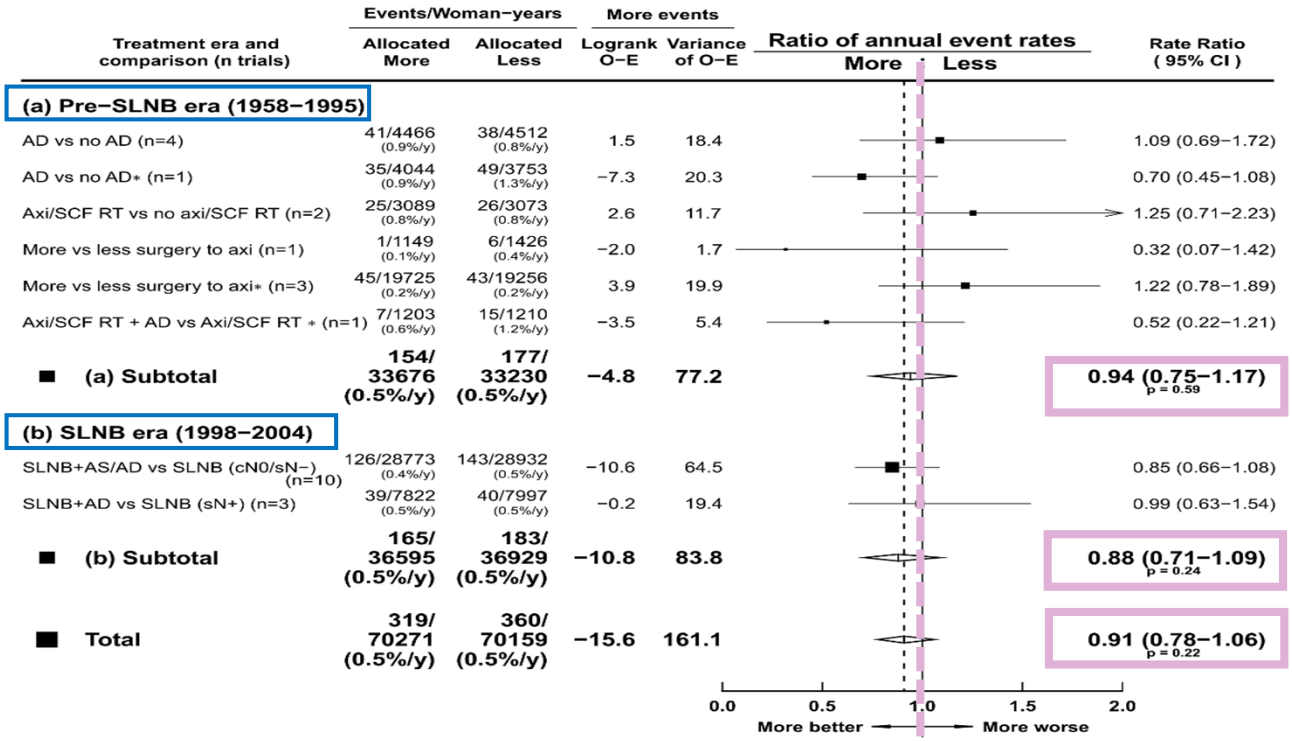
SABCS 2023: EBCTCG/Oxford Meta-analysis Overview of Axillary Trials in Early BC

- Meta-analysis of randomized trials of axillary management
- PIII trials: 1958-2004 ALND, Ax-RT, SLNB
- Trials N=30 Patients N=20,285
  - Analysis of Pre-SLNB era & SLNB era
    - More vs Less axillary treatment
    - Axillary dissection vs axillary radiotherapy

Mannu et al for EBCTCG, SABCS 2023

EBCTCG SABCS 2023: More vs Less Ax-Treatment

Annual Events by N-status & Era

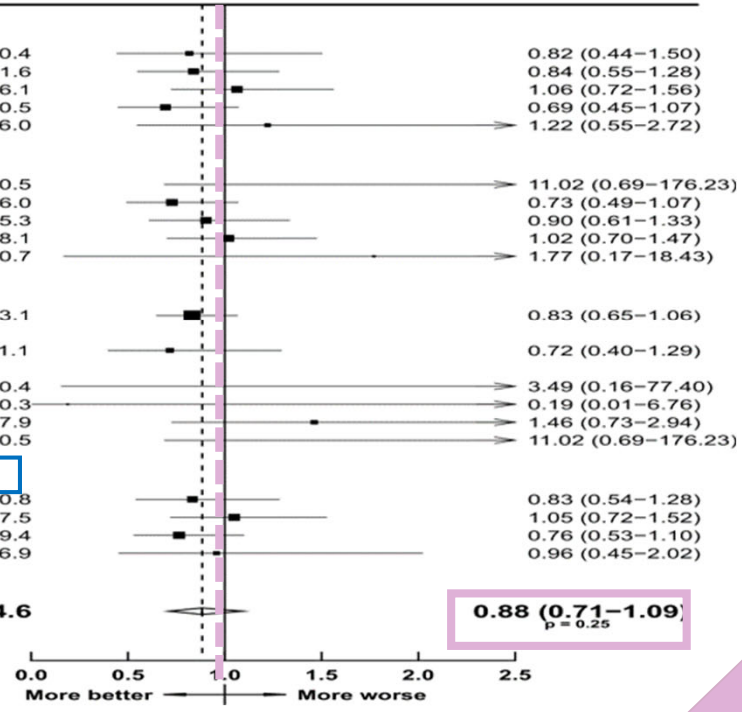


Mannu et al for EBCTCG, SABCS 2023

EBCTCG SABCS 2023: More vs Less Ax-Treatment

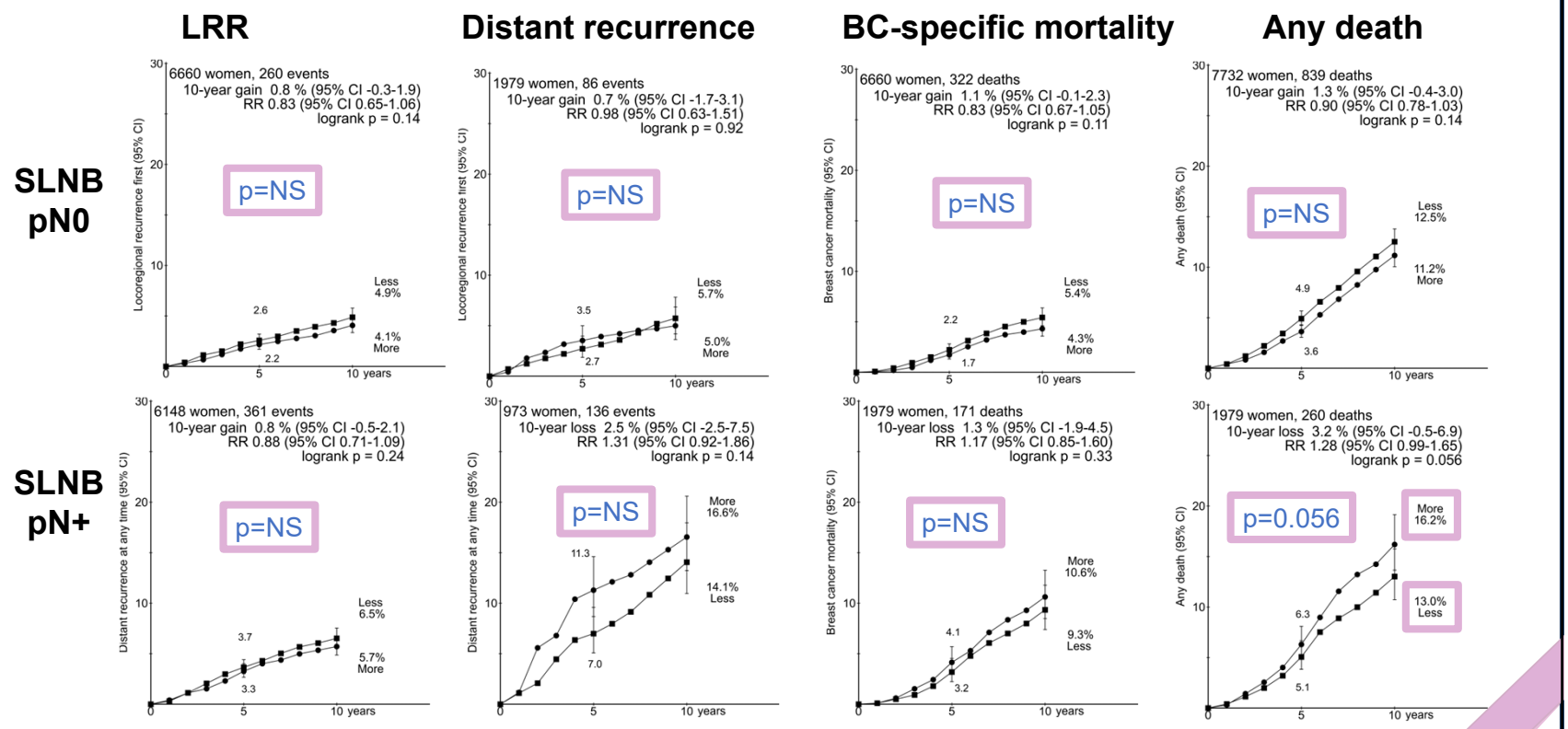
LRR in SLNB trials

Category	Events/Women: Allocated More	Events/Women: Allocated Less	More events: Logrank O−E	More events: Variance of O−E	Rate Ratio (95% CI)
(a) Age at entry (χ^2_1 = 0.0; p = 0.87)					
Age < 40 yrs	21/231	25/227	−2.1	10.4	0.82 (0.44−1.50)
Age 40 − 49 yrs	43/947	46/929	−3.8	21.6	0.84 (0.55−1.28)
Age 50 − 59 yrs	53/1408	53/1517	1.6	26.1	1.06 (0.72−1.56)
Age 60 − 69 yrs	35/1279	48/1205	−7.5	20.5	0.69 (0.45−1.07)
Age 70+ yrs	13/592	11/606	1.2	6.0	1.22 (0.55−2.72)
(b) Number of SNs excised (χ^2_1 = 0.8; p = 0.38)					
0	2/140	0/117	1.2	0.5	11.02 (0.69−176.23)
1	45/1520	62/1544	−8.3	26.0	0.73 (0.49−1.07)
2	48/1229	65/1332	−2.6	25.3	0.90 (0.61−1.33)
3−10	68/1507	55/1448	0.5	28.1	1.02 (0.70−1.47)
Other/unknown	2/61	1/43	0.4	0.7	1.77 (0.17−18.43)
(c) SNB status (χ^2_4 = 4.1; p = 0.39)					
SNB negative	118/3297	142/3363	−11.7	63.1	0.83 (0.65−1.06)
ITC	0/8	0/10			
Micromets	19/558	26/568	−3.7	11.1	0.72 (0.40−1.29)
1 macromets	1/15	0/14			
2 macromets	2/11	1/6	0.5	0.4	3.49 (0.16−77.40)
3+ macromets	4/10	1/1	−0.5	0.3	0.19 (0.01−6.76)
Positive only	19/391	13/387	3.0	7.9	1.46 (0.73−2.94)
Unknown	2/167	0/135	1.2	0.5	11.02 (0.69−176.23)
(d) Period of follow−up (woman−years) (χ^2_1 = 0.0; p = 0.83)					
Years 0−1	40/8447	46/8535	−3.8	20.8	0.83 (0.54−1.28)
Years 2−4	58/11262	55/11400	1.3	27.5	1.05 (0.72−1.52)
Years 5−9	52/13867	67/14025	−7.9	29.4	0.76 (0.53−1.10)
Years 10+	15/3020	15/2968	−0.3	6.9	0.96 (0.45−2.02)
Total	**165/ 4457 (3.7%)**	**183/ 4484 (4.1%)**	**−10.6**	**84.6**	**0.88 (0.71−1.09) p = 0.25**



Mannu et al for EBCTCG, SABCS 2023

EBCTCG SABCS 2023:
More vs Less Ax-Treatment by N-status in SLNB Trials

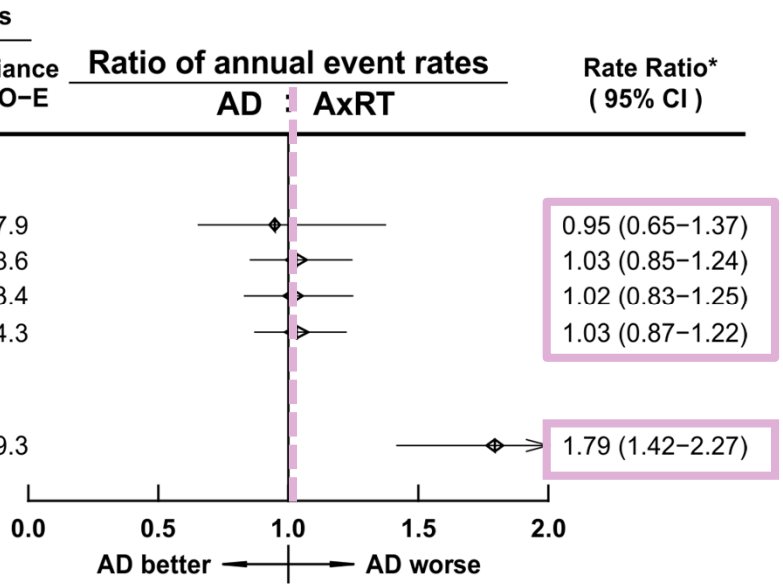


Mannu et al for EBCTCG, SABCS 2023

EBCTCG SABCS 2023: Ax-dissection vs Ax-radiotherapy

Summary of outcomes

Outcome	Events/Women: Allocated AD	Events/Women: Allocated AxRT	AD events: Logrank O−E	AD events: Variance of O−E	Rate Ratio* (95% CI)
Recurrence and mortality					
Locoregional recurrence	59/1235	58/1124	−1.5	27.9	0.95 (0.65−1.37)
Distant recurrence	252/1235	229/1124	3.3	108.6	1.03 (0.85−1.24)
Breast cancer mortality	227/1235	197/1124	1.7	93.4	1.02 (0.83−1.25)
Any death	323/1235	286/1124	4.2	134.3	1.03 (0.87−1.22)
Morbidity					
Any lymphoedema	263/612	174/592	40.5	69.3	1.79 (1.42−2.27)



■ 95% or ◇ 95% confidence intervals

* odds ratio for lymphoedema

Mannu et al for EBCTCG, SABCS 2023

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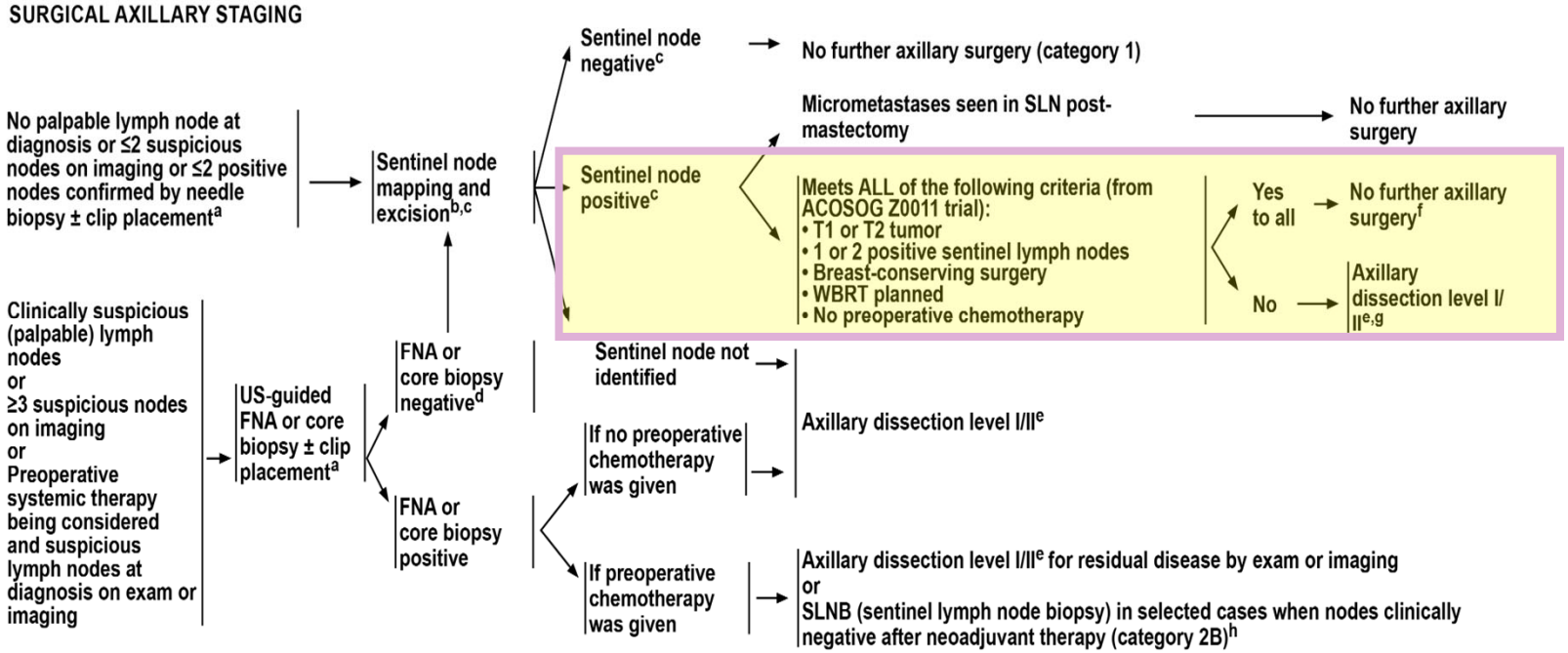

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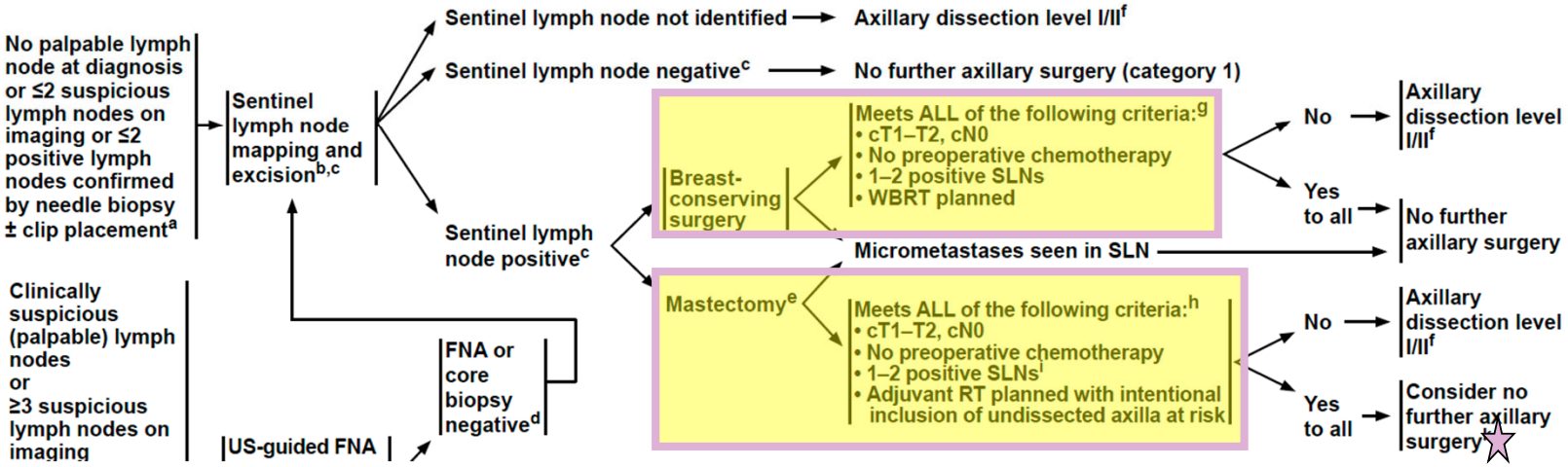
CONSIDERATIONS FOR SURGICAL AXILLARY STAGING



[k]In the mastectomy setting, in patients who were initially cN0 who have pN+SLNB, and have no axillary dissection, RT to the chest wall should include the undissected axilla at risk +/- RNI

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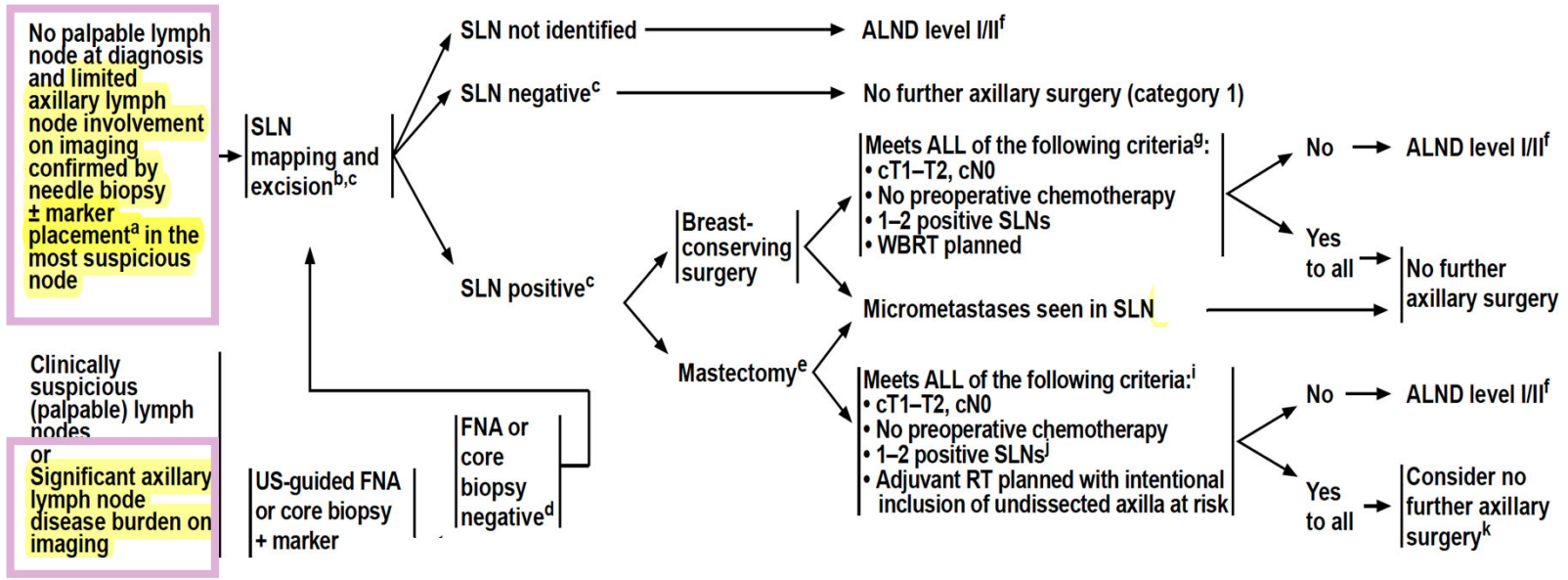
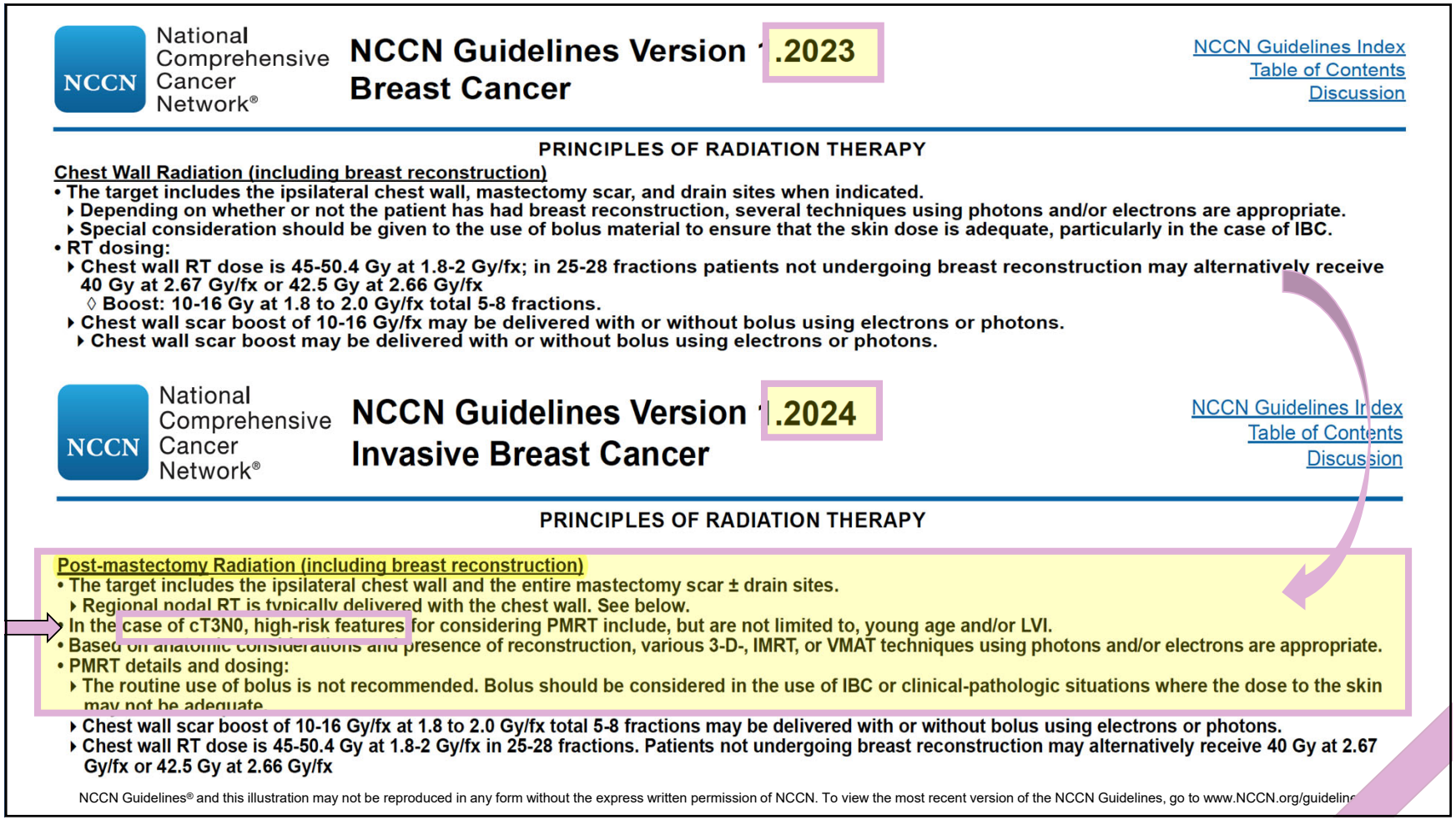
CONSIDERATIONS FOR SURGICAL AXILLARY STAGING



BINV-I:
Principles of Radiation Therapy



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PRINCIPLES OF RADIATION THERAPY

Chest Wall Radiation (including breast reconstruction)

- The target includes the ipsilateral chest wall, mastectomy scar, and drain sites when indicated.
  - Depending on whether or not the patient has had breast reconstruction, several techniques using photons and/or electrons are appropriate.
  - Special consideration should be given to the use of bolus material to ensure that the skin dose is adequate, particularly in the case of IBC.
- RT dosing:
  - Chest wall RT dose is 45-50.4 Gy at 1.8-2 Gy/fx; in 25-28 fractions patients not undergoing breast reconstruction may alternatively receive 40 Gy at 2.67 Gy/fx or 42.5 Gy at 2.66 Gy/fx
    - ◊ Boost: 10-16 Gy at 1.8 to 2.0 Gy/fx total 5-8 fractions.
  - Chest wall scar boost of 10-16 Gy/fx may be delivered with or without bolus using electrons or photons.
    - Chest wall scar boost may be delivered with or without bolus using electrons or photons.

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PRINCIPLES OF RADIATION THERAPY

Post-mastectomy Radiation (including breast reconstruction)

- The target includes the ipsilateral chest wall and the entire mastectomy scar ± drain sites.
  - Regional nodal RT is typically delivered with the chest wall. See below.
- In the case of cT3N0, high-risk features for considering PMRT include, but are not limited to, young age and/or LVI.
- Based on anatomic considerations and presence of reconstruction, various 3-D-, IMRT, or VMAT techniques using photons and/or electrons are appropriate.
- PMRT details and dosing:
  - The routine use of bolus is not recommended. Bolus should be considered in the use of IBC or clinical-pathologic situations where the dose to the skin may not be adequate
  - Chest wall scar boost of 10-16 Gy/fx at 1.8 to 2.0 Gy/fx total 5-8 fractions may be delivered with or without bolus using electrons or photons.
  - Chest wall RT dose is 45-50.4 Gy at 1.8-2 Gy/fx in 25-28 fractions. Patients not undergoing breast reconstruction may alternatively receive 40 Gy at 2.67 Gy/fx or 42.5 Gy at 2.66 Gy/fx

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PMRT for T3N0

T3N0 ⌀PMRT: Review of 5 NSABP Trials

N=312

Tumor Size	Pts #	Isolated LRF	Any LRF
5 cm	144	7%	10%
5.1-7 cm	130	9%	10%
> 7 cm	39	3%	10%

Taghian A. et al; J Clin Onc 2006

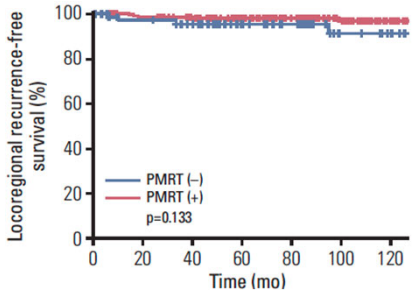
USA Multi-institutional Review T3N0

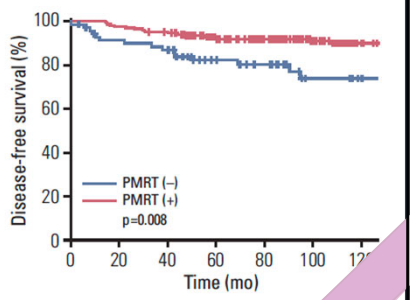
- N=70 T3 N0 3 institutions
- 1981-2002 Med F/u=85 mo
- LRR=7.6% @ 5 yrs
- +LVI only factor significant for LRR, DFS and OS

Floyd SR et al; Int J Rad Oncol Bio Phys 2006

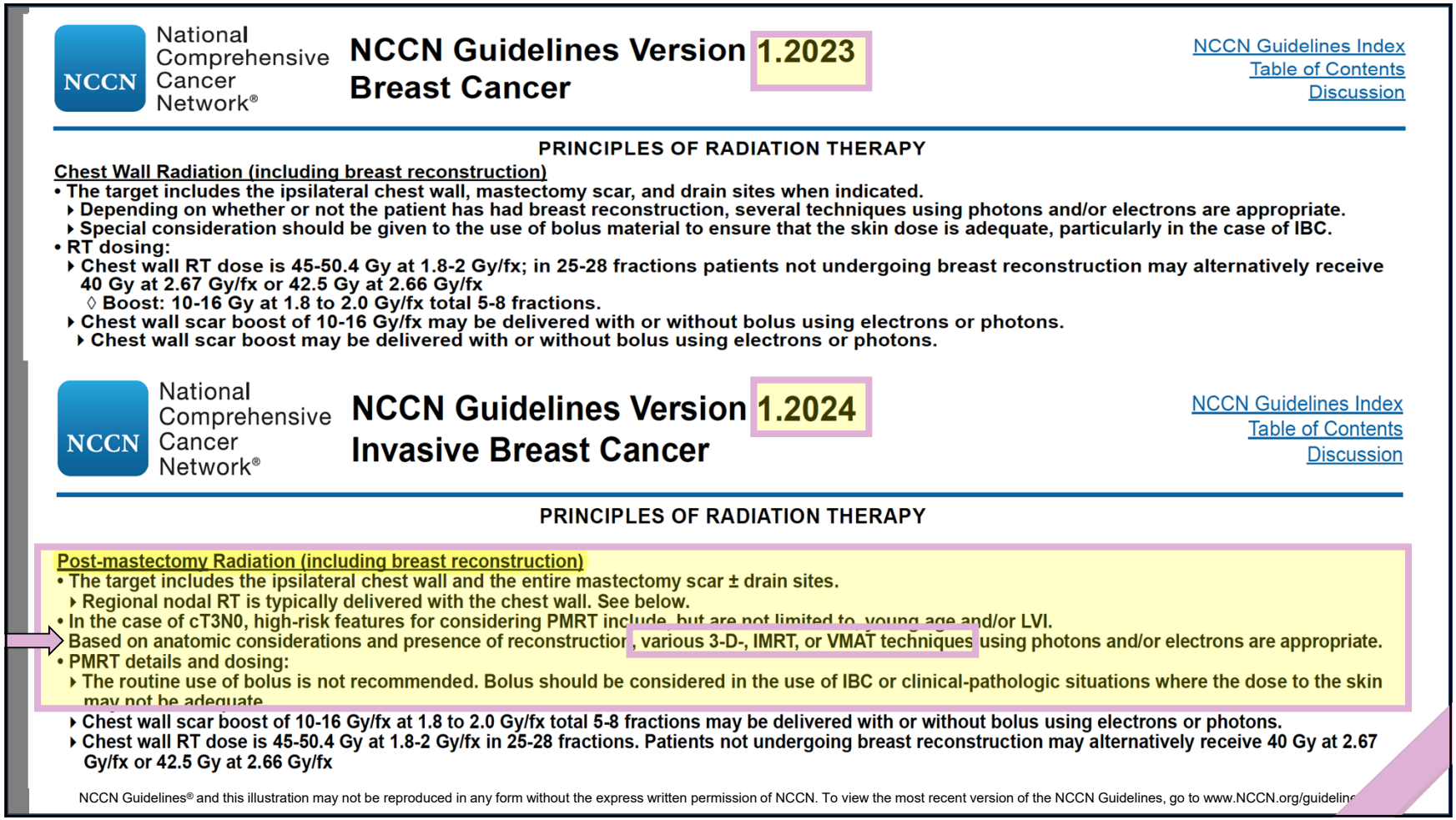
KROG 20-03, T3,N0 +/-PMRT

- T3N0 s/p Mast, N=274, **18 institutions**
- 2000-2016 Med f/u=8 yrs (95 months)
- ~90% had chemotherapy, ~70% had ET
- 8-yr LRFS:PMRT 98.0% vs. ⌀PMRT 91.3%, p=0.133
- 8-yr DFS: PMRT 91.3% vs. ⌀PMRT 73.9%, p=0.008
- On MVA, only +PMRT & +LVI predictive of DFS
- Conclusion: T3N0 LRR low (<10%) +/-PMRT, but PMRT may have DFS effects





Kim K, et al. Cancer Res Treat. 2022



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NCCN Guidelines Version 1.2023
Breast Cancer

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PRINCIPLES OF RADIATION THERAPY

Chest Wall Radiation (including breast reconstruction)

- The target includes the ipsilateral chest wall, mastectomy scar, and drain sites when indicated.
  - Depending on whether or not the patient has had breast reconstruction, several techniques using photons and/or electrons are appropriate.
  - Special consideration should be given to the use of bolus material to ensure that the skin dose is adequate, particularly in the case of IBC.
- RT dosing:
  - Chest wall RT dose is 45-50.4 Gy at 1.8-2 Gy/fx; in 25-28 fractions patients not undergoing breast reconstruction may alternatively receive 40 Gy at 2.67 Gy/fx or 42.5 Gy at 2.66 Gy/fx
    - ◊ Boost: 10-16 Gy at 1.8 to 2.0 Gy/fx total 5-8 fractions.
  - Chest wall scar boost of 10-16 Gy/fx may be delivered with or without bolus using electrons or photons.
    - Chest wall scar boost may be delivered with or without bolus using electrons or photons.

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PRINCIPLES OF RADIATION THERAPY

Post-mastectomy Radiation (including breast reconstruction)

- The target includes the ipsilateral chest wall and the entire mastectomy scar ± drain sites.
  - Regional nodal RT is typically delivered with the chest wall. See below.
- In the case of cT3N0, high-risk features for considering PMRT include, but are not limited to, young age and/or LVI.
- Based on anatomic considerations and presence of reconstruction, various 3-D-, IMRT, or VMAT techniques using photons and/or electrons are appropriate.
- PMRT details and dosing:
  - The routine use of bolus is not recommended. Bolus should be considered in the use of IBC or clinical-pathologic situations where the dose to the skin may not be adequate.
  - Chest wall scar boost of 10-16 Gy/fx at 1.8 to 2.0 Gy/fx total 5-8 fractions may be delivered with or without bolus using electrons or photons.
  - Chest wall RT dose is 45-50.4 Gy at 1.8-2 Gy/fx in 25-28 fractions. Patients not undergoing breast reconstruction may alternatively receive 40 Gy at 2.67 Gy/fx or 42.5 Gy at 2.66 Gy/fx

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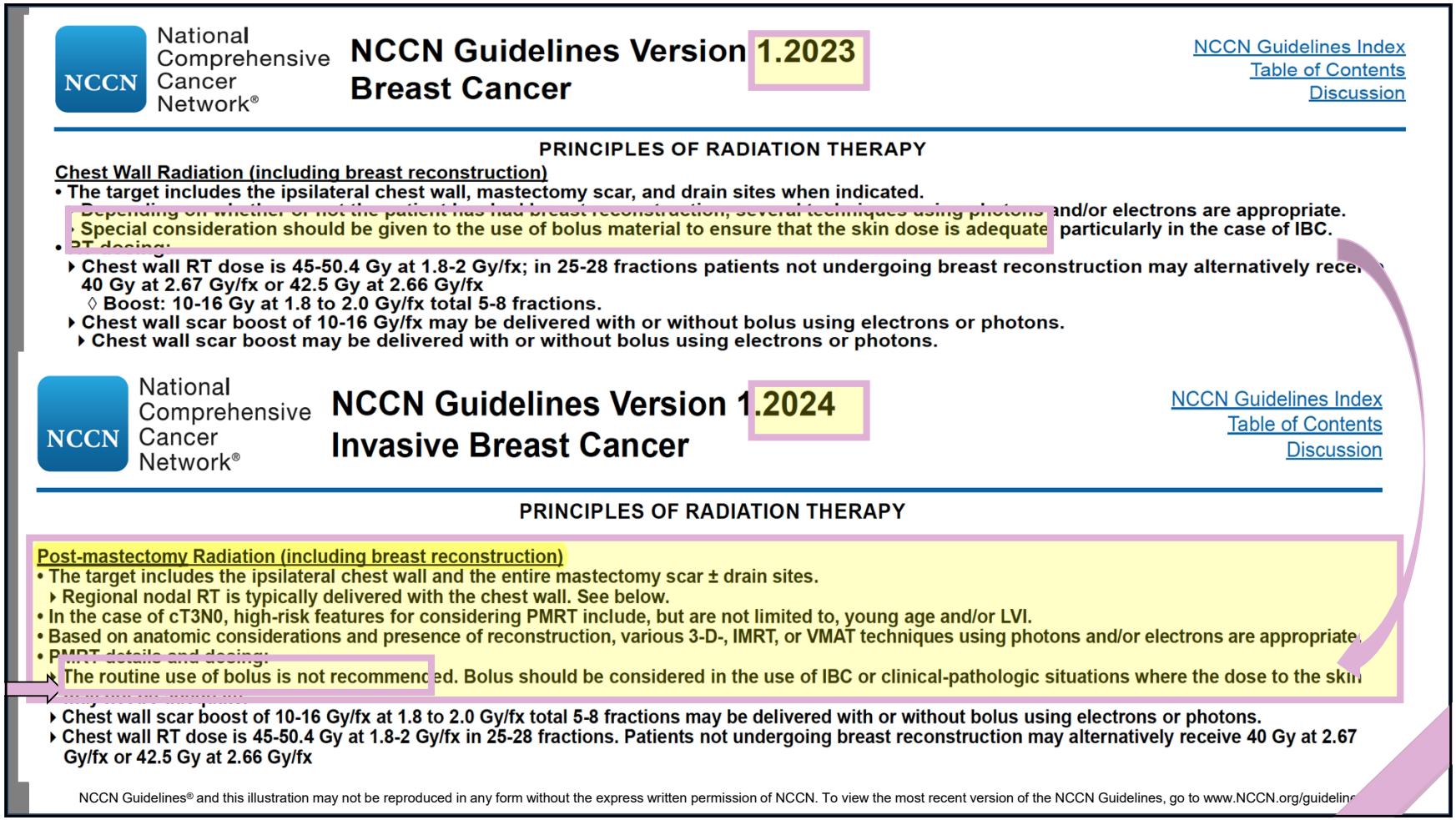

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Bolus Meta-analysis

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

The use of bolus in postmastectomy radiation therapy for breast cancer: systematic review

Hannah M. Dahn [a,*], Liesbeth J. Boersma [b], Dirk de Ruysscher [b], Icro Meattini [c], Birgitte V. Offersen [d], Jean-Philippe Pignol [a], Cynthia Aristei [e], Yazid Belkacemi [f,g], Dori Benjamin [h], Nuran Bese [i], Charlotte E. Coles [j], Pierfrancesco Franco [k,l], Alice Ho [m], Sandra Hol [n], Reshma Jagsi [o], Anna M. Kirby [q], Livia Marrazzo [p], Gustavo N. Marta [r], Meena S. Moran [s], Alan M. Nichol [t], Henrik D. Nissen [u], Vratislav Strnad [v], Yvonne E. Zissiadis Philip Poortmans [x], Orit Kaidar-Person [y,z]

- 27 retrospective studies
- Bolus grade III acute RT dermatitis
  - 9.6% +bolus vs. 1.2% ⌀bolus
- Pooled crude LR rates
- LR +Bolus 3.5% vs. 3.6% ⌀ Bolus

Bolus Consensus Panel

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Recommendation

A Delphi study and International Consensus Recommendations: The use of bolus in the setting of postmastectomy radiation therapy for early breast cancer

Orit Kaidar-Person [a,b,*], Hannah M. Dahn [c], Alan M. Nichol [d], Liesbeth J. Boersma [e], Dirk de Ruysscher [e], Icro Meattini [f], Jean-Philippe Pignol [c], Cynthia Aristei [g], Yazid Belkacemi [h,l], Dori Benjamin [i], Nuran Bese [j], Charlotte E. Coles [k], Pierfrancesco Franco [l], Alice Y. Ho [m], Sandra Hol [n], Reshma Jagsi [o], Anna M. Kirby [p], Livia Marrazzo [q], Gustavo N. Marta [r], Meena S. Moran [s,l], Henrik D. Nissen [t], Vratislav Strnad [u], Yvonne Zissiadis [v], Philip M. Poortmans [w], Birgitte V. Offersen [x]

- Bolus ↑ PMRT acute effects significantly
- Bolus: no effects on LC *unless risk of skin involvement
- Recommendation: Bolus should only be used for:
  - IBC or Skin involvement (stage T4b, c, d)
  - Inoperable or fungating masses
  - Superficial/anterior + margins (DCIS/invasive)
  - Treatment of chest wall local recurrences

2022 Modification: Addition of Sequencing of RT with Systemic Agents Added

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NCCN Guidelines Version 2.2022
Invasive Breast Cancer

PRINCIPLES OF RADIATION THERAPY

RT with Preoperative or Adjuvant Systemic Therapy

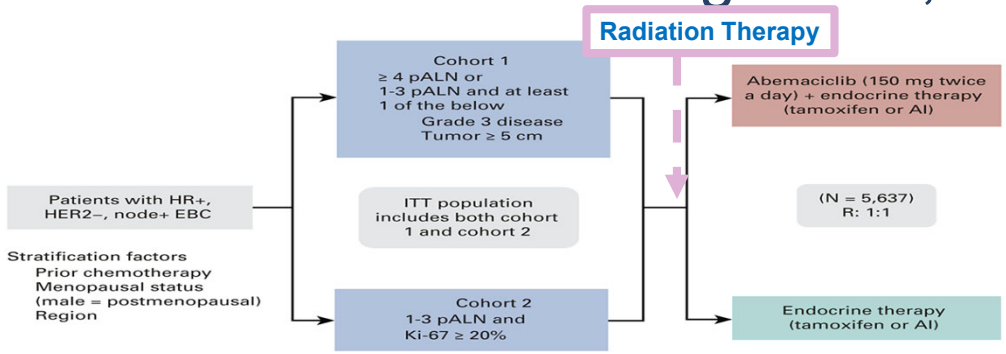
- In patients treated with preoperative systemic therapy, adjuvant RT is based on the maximal disease stage (ie, clinical stage, pathologic stage, tumor characteristics) at diagnosis (before preoperative systemic therapy) and pathology results after preoperative systemic therapy.
- Sequencing of RT with systemic therapy:
  - ◊ It is common for RT to follow chemotherapy when chemotherapy is indicated. However,
    - CMF (cyclophosphamide/methotrexate/fluorouracil) and RT may be given concurrently, or CMF may be given first.
    - Capecitabine should be given after completion of RT.
    - Olaparib should be given after completion of RT.
  - ◊ Available data suggest that sequential or concurrent endocrine therapy with RT is acceptable. Due to compounding side effects, initiating endocrine therapy at the completion of RT may be preferred.
  - ◊ Adjuvant HER2-targeted therapy ± endocrine therapy may be delivered concurrently with RT.

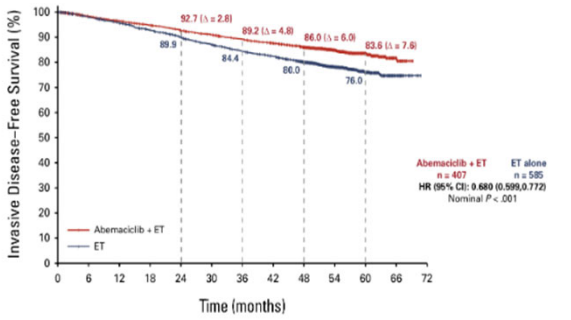
Did not comment on Abemaciclib

CDK 4/6 Inhibitors

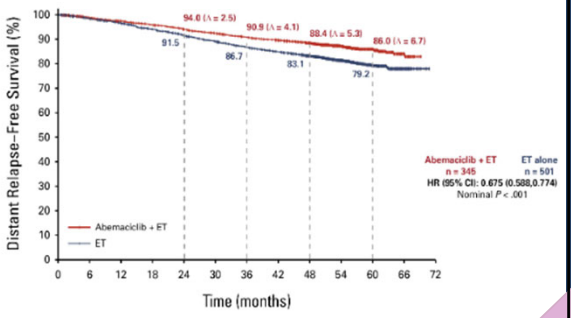
- The routine use of CDK 4/6 inhibitors for early-stage, high-risk BC not well established several years ago
- More recent data have support the use of Abemaciclib in early-stage disease
- No large-scale or phase 3 safety & efficacy data of concomitant CDK 4/6i + RT
  - Case reports
  - Retrospective reviews
- PIII protocols of trials establishing CDK4/6 inhibitor use typically did not deliver CDK4/6i w/ RT
  - Definitive
  - Palliative setting

MonarchE
Abemaciclib in High-Risk, ER+/HER2- BC





Outcome, %	Abemaciclib + ET (n = 2808)	ET Alone (n = 2829)	Absolute Difference Between Arms	Hazard Ratio (85% CI)	Nominal P Value
iDFS rates over time				0.680 (0.599-0.772)	<.001
▪ Yr 2	92.7	89.9	2.8		
▪ Yr 3	89.2	84.4	4.8		
▪ Yr 4	86.0	80.0	6.0		
▪ Yr 5	83.6	76.0	7.6		
DRFS rates over time				0.675 (0.588-0.774)	<.001
▪ Yr 2	94.0	91.5	2.5		
▪ Yr 3	90.9	86.7	4.1		
▪ Yr 4	88.4	83.1	5.3		
▪ Yr 5	86.0	79.2	6.7		



Sequencing of Abemaciclib with RT

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Invasive Breast Cancer

PRINCIPLES OF RADIATION THERAPY

RT with Preoperative or Adjuvant Systemic Therapy

- In patients treated with preoperative systemic therapy, adjuvant RT is based on the maximal disease stage (ie, clinical stage, pathologic stage, tumor characteristics) at diagnosis (before preoperative systemic therapy) and pathology results after preoperative systemic therapy.
- Sequencing of RT with systemic therapy:
  - It is common for RT to follow chemotherapy when chemotherapy is indicated. However,
    - CMF (cyclophosphamide/methotrexate/fluorouracil) is the only standard regimen that can be given concurrently with RT.
    - Capecitabine is typically given after completion of RT.
    - Olaparib should be given after completion of RT.
  - Available data suggest that sequential or concurrent endocrine therapy with RT is acceptable. Due to compounding side effects, initiating endocrine therapy at the completion of RT may be preferred.
    - Abemaciclib should be initiated after completion of surgery/RT/chemotherapy, concurrently with endocrine therapy.
  - Adjuvant HER2-targeted therapy ± endocrine therapy may be delivered concurrently with RT.

BIN

BINV-F:
Margin Status Recommendations After BCT

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Invasive Breast Cancer

MARGIN STATUS RECOMMENDATIONS AFTER BCS FOR INVASIVE CANCERS AND DCIS

Invasive Breast Cancer

- For invasive breast cancers that have a component of DCIS, regardless of the extent of DCIS, the negative margin definition of "no ink on tumor" should be based on the invasive margin guideline. In this setting, "no ink on tumor" is recommended for either DCIS or invasive cancer cells, primarily because the natural history, treatment, and outcomes of these lesions are more similar to invasive cancer than DCIS. For specifically challenging cases, clinical judgment and discussion with the patient should precede routine re-excision.
- These margin recommendations cannot be applied directly to patients undergoing APBI/PBI,[1] where data regarding local recurrence are more limited. Furthermore, individualized clinical judgment should be utilized on a case-by-case basis, using postoperative mammography to identify residual calcifications and clinical-pathologic factors such as quantitative extent of disease near margin, presence of extensive intraductal component (EIC),[3] young age, or multiple close margins to assist in identifying patients who may have an increased risk of IBTR and therefore may be selected to benefit from re-excision.
- For patients with invasive breast cancer after BCS, with microscopically focally positive margins (in the absence of an EIC),[3] the use of a higher radiation boost dose to the tumor bed may be considered, since generally a boost to the tumor bed is recommended for patients at higher risk of recurrence. See BINV-I.

	No ink on tumor	2-mm margin	No margin necessary
Invasive breast cancer	X		
Invasive breast cancer + DCIS	X		
Invasive breast cancer + extensive DCIS	X		
Pure DCIS		X	
DCIS with microinvasion		X	
Pure LCIS* at surgical margin			X
Atypia at surgical margin			X

*For pleomorphic Lobular Carcinoma In Situ (LCIS), the optimal width of margins is not known.

Meta-analysis did not include studies of margins in Neoadjuvant setting

[1] Moran MS, Schnitt SJ, Giuliano AE, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for BCS with whole-breast irradiation in stages I and II invasive breast cancer. J Clin Oncol 2014;32:1507-1515.

[3] EIC is defined as an infiltrating ductal cancer where >25% of the tumor volume is DCIS and DCIS extends beyond the invasive cancer into surrounding normal breast parenchyma.

SSO/ASTRO Margins Consensus for Invasive Cancers Undergoing BCS Did Not Address Margins After Primary Neoadjuvant Therapy (NAT)

- Limited data (2011) for assessing margins after NAT for the invasive margins meta-analysis
- Subsequent ↑ use of NAT→ ↑publications assessing margins w/NAT in invasive BCS setting
- Vast majority are observational/institutional series
- Suggest wider margin widths did not result in better LRFS, DFS or OS

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Invasive Breast Cancer

MARGIN STATUS RECOMMENDATIONS AFTER BCS FOR INVASIVE CANCERS AND DCIS

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	No ink on tumor	2-mm margin	No margin necessary
Invasive breast cancer	X		
Invasive breast cancer + DCIS	X		
Invasive breast cancer + extensive DCIS	X		
Invasive breast cancer (treated with neoadjuvant chemotherapy followed by breast conservation therapy)[4,5]	X		
Pure DCIS		X	
DCIS with microinvasion		X	
Pure LCIS* at surgical margin			X
Atypia at surgical margin			X

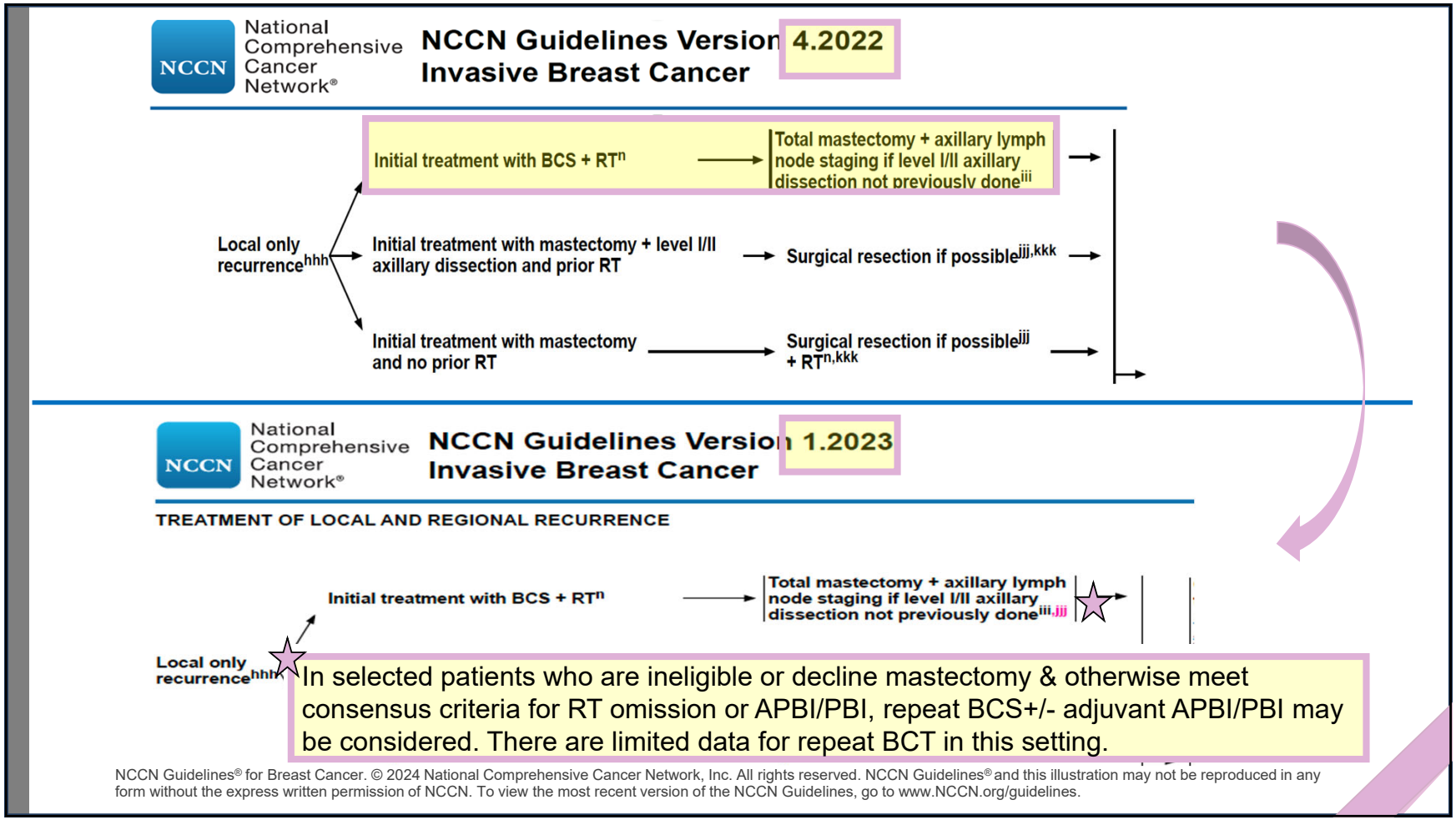
*For pleomorphic Lobular Carcinoma In Situ (LCIS), the optimal width of margins is not known.

[1] Moran MS, Schnitt SJ, Giuliano AE, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. J Clin Oncol 2014;32:1507-1515.
[3] EIC is defined as an infiltrating ductal cancer where >25% of the tumor volume is DCIS and DCIS extends beyond the invasive cancer into surrounding normal breast parenchyma.
[4] Choi J, Laws A, Hu J, et al. Margins in breast-conserving surgery after neoadjuvant therapy. Ann Surg Oncol 2018;25:3541-3547.
[5] Wimmer K, Bolliger M, Bago-Horvath Z, et al. Impact of surgical margins in breast cancer after preoperative systemic chemotherapy on local recurrence and survival. Ann Surg Oncol 2020;27:1700-1707.

BINV-19 & BINV-20: Treatment of Local & Regional Recurrence

Management of Ipsilateral Breast Tumor Recurrence (IBTR) after BCT (BCS + WBRT)

- Most common type of recurrence is local
- Isolated IBTR (without distant dx) have the potential for durable, long-term responses after additional local-regional treatment and systemic therapy
- Mastectomy (+/- RT) remains the surgical standard of care for most patients with IBTR after BCT
- Some limited data suggests a carefully selected cohort could be treated w/repeat BCT
- Most of data for repeat BCT consist of retrospective series & 1 phase II study (RTOG 1014)



NRG Oncology/RTOG 1014

Phase II single-arm, prospective trial

- Evaluated effectiveness & adverse effects of
- 3D-EBRT PBI after 2nd lumpectomy for IBTR for pts with IBTR & previous BCS+WBRT
- Median F/u: 5.5 years
- N=65 (58 evaluable)
- Eligibility:
  - < 3cm size
  - Unifocal
  - >1 yr interval to IBTR
  - negative margins at repeat BCS

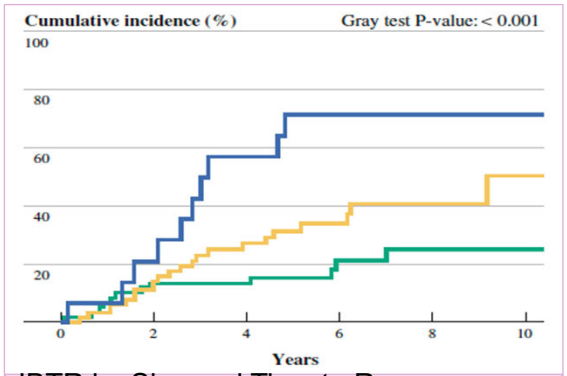
Intervention:
PBI-1.5 Gy BID→ 45 Gy (30 fx)

Results:
- 2nd IBTR @ median 5.5 yrs=5.2%
- 5 yr OS=94.8%
- 7% G3 RT-related toxicity (breast/skin fibrosis)no G4 or G5

Arthur D, et al. JAMA Onc Jan 2020

Milan Repeat BCT Series

- N=161 F/U: 5.5 years
- Retrospective, single institutional series
- Who are the best candidates for repeat BCT for IBTR after previous BCS+WBRT ?



IBTR by Size and Time to Recurrence
>2cm 5yr: 71.2%
≤2cm + Time IBTR ≤48 mo 5 yr: 31.2%
≤2cm + Time IBTR 48 mo 5 yr: 15.2%

Gentilini O et al. Ann Surg Onc 2012

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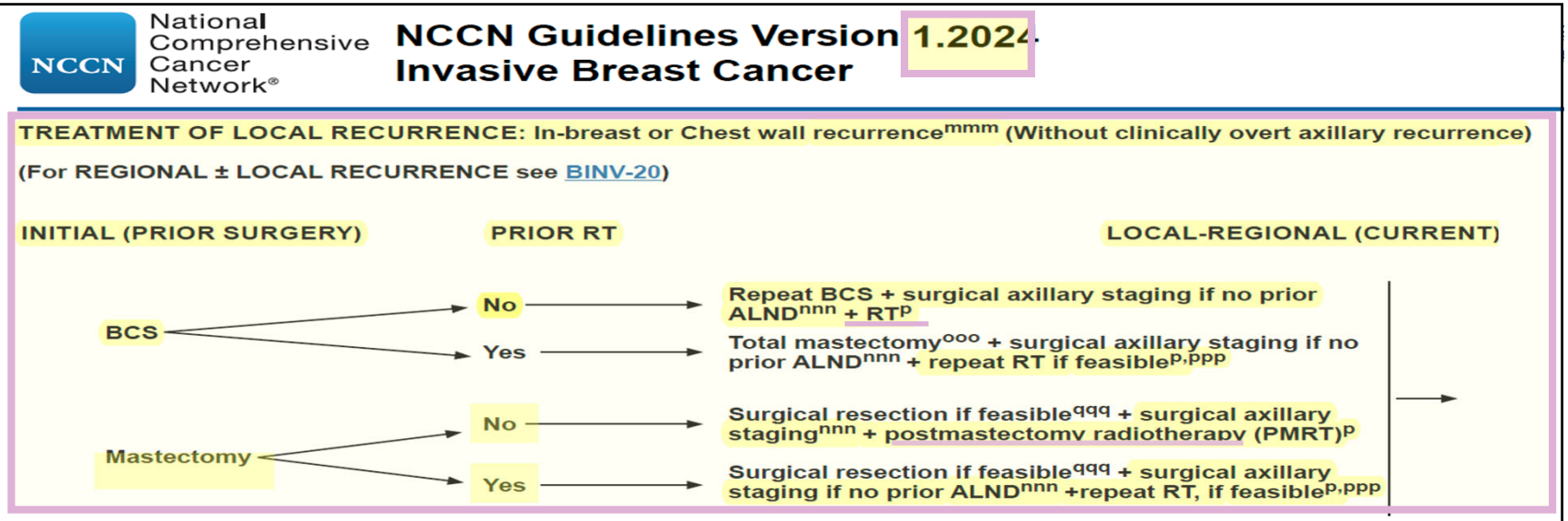
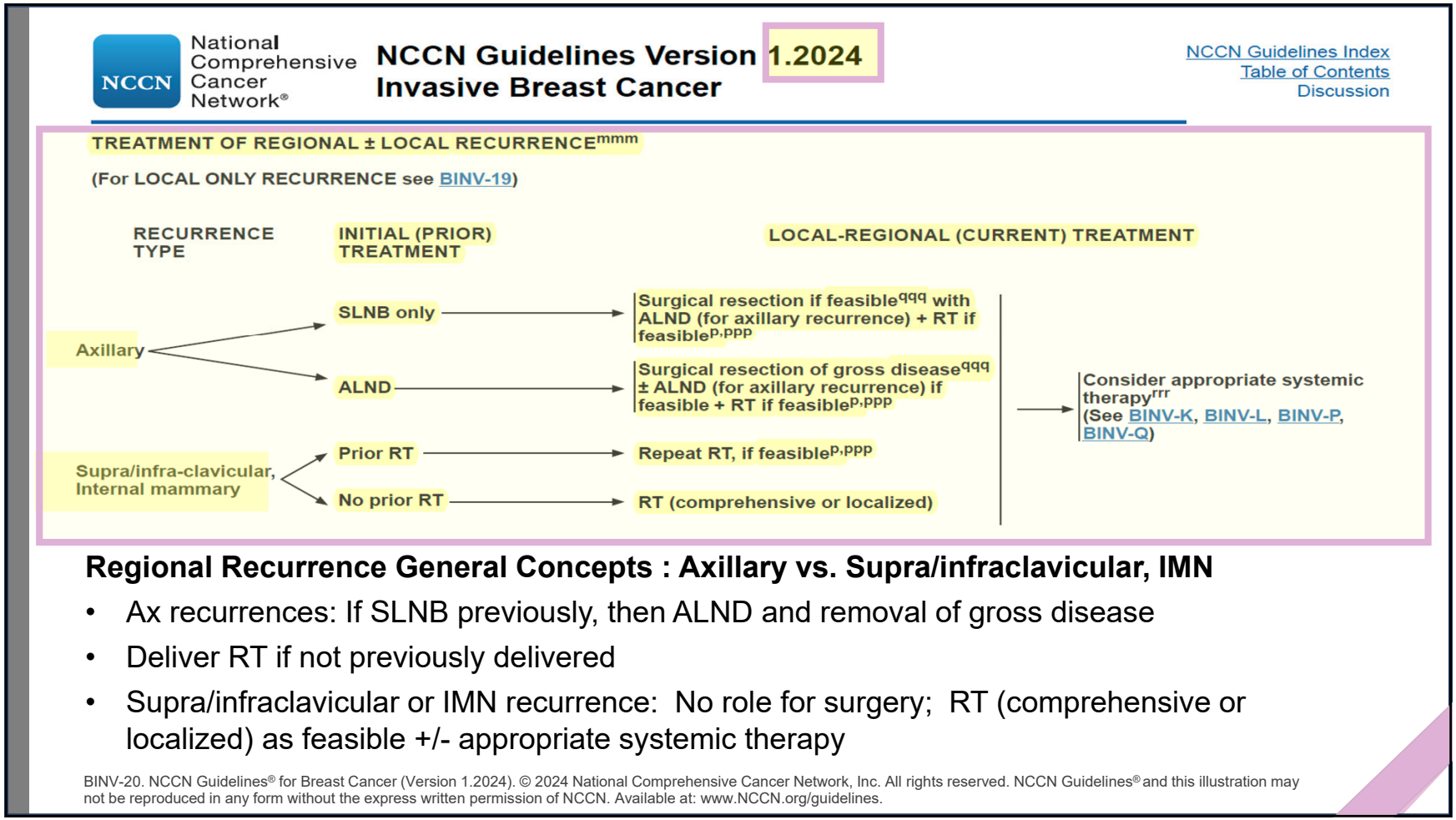


General Concepts (in-breast or chest wall recurrence):

- Maximal resection/surgery, if feasible
  - Use systemic therapy to maximal response for cytoreduction
- If prior BCT, then Mastectomy is SOC

  *can consider repeat BCS +/ - APBI/PBI
- Axilla: surgical assessment if no prior ALND
- Give RT at recurrence if not previously delivered (BCS or Mastectomy)
- Can consider re-irradiation, as feasible, taking into consideration cumulative doses from prior and intended treatment, to determine risk vs. benefit



Regional Recurrence General Concepts : Axillary vs. Supra/infraclavicular, IMN

- Ax recurrences: If SLNB previously, then ALND and removal of gross disease
- Deliver RT if not previously delivered
- Supra/infraclavicular or IMN recurrence: No role for surgery; RT (comprehensive or localized) as feasible +/- appropriate systemic therapy

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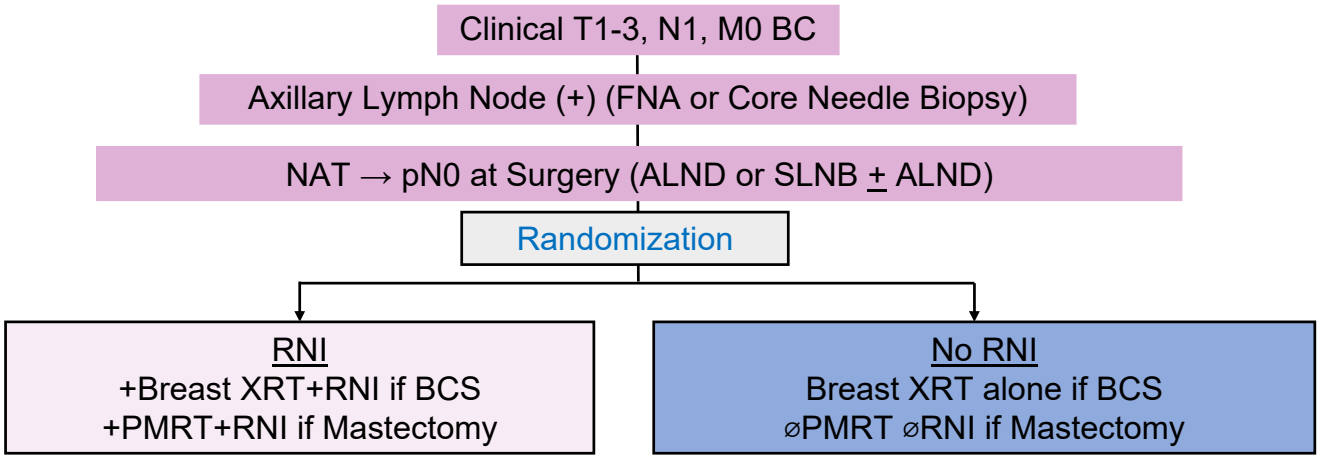
Radiation in the NAT Setting

SABCS 2023:
Preliminary 5 Year Outcomes of NSABP B-51 Trial



Mamounas, T et al SABCS 2023 Abstract GS02-0

Results B51

Results:

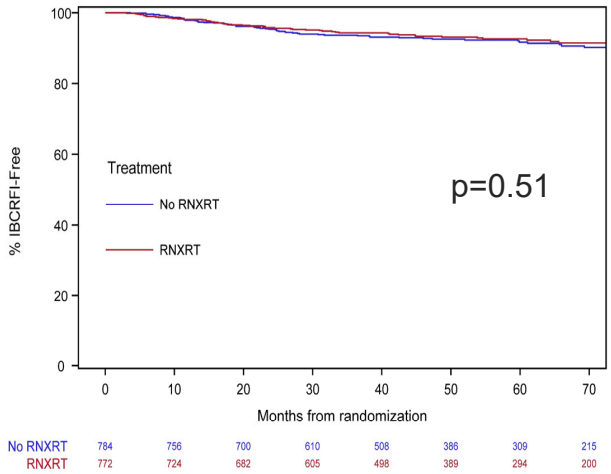
- Median Follow-up Time: 59.5 months
- N=1556 patients analyzed No RNI=784 RNI=772

Patient Characteristics		No RNI (%) n=821	RNI (%) n=820
Tumor Subtype	Triple-negative ER+ and/or PR+/HER2- ER- and PR-/HER2+ ER+ and/or PR+/HER2+	21 22 25 31	23 20 24 33
Breast Surgery	Lumpectomy Mastectomy	58 42	58 42
Axillary Surgery	SLNB ALND (+/-SLNB)	55 45	56 44
pCR in Breast	No Yes	22 78	21 79
Adjuvant Chemotherapy	No Yes	100 <1	99 1

Mamounas, T et al SABCS 2023 Abstract GS02-07

Results B51

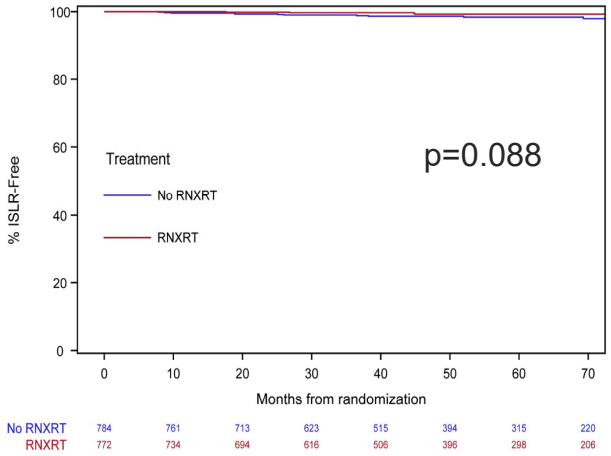
Invasive Breast Cancer Recurrence-free Interval (IBCRFI)



	No RNI	RNI
# Events	59	50
HR (95%CI), p-v	0.88 (0.60-1.29)	
5-Year Estimate	91.8%	92.7%

Isolated Loco-Regional Recurrence-free Interval (ILRRFI)*

***LRR w/ no distant dx within 2 mos**

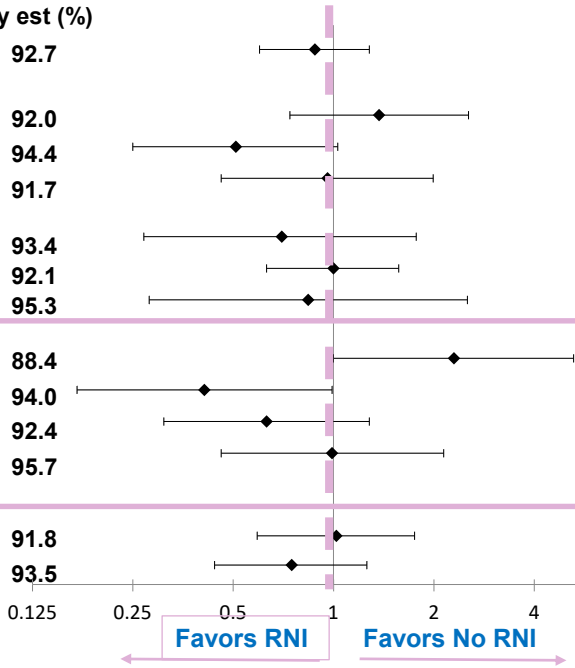


	No RNI	RNI
# Events	11	4
HR (95%CI), p-v	0.37 (0.12-1.16)	
5-Year Estimate	98.4%	99.3%

Mamounas, T et al SABCS 2023 Abstract GS02-07

IBCRFI – Exploratory Subgroup Analysis B-51

Variable		No RNI (D/N)	No RNI 5-y est (%)	RNI (D/N)	RNI 5-y est (%)	HR (95% CI)	P-interaction
	All patients	59/784	**91.8**	50/772	**92.7**	**0.88** (0.60,1.28)	
Age	<=49	18/311	**92.8**	24/312	**92.0**	**1.37** (0.74,2.54)	0.09
	50-59	25/257	**90.4**	12/254	**94.4**	**0.51** (0.25,1.03)	
	>= 60	16/216	**92.4**	14/206	**91.7**	**0.96** (0.46,1.99)	
Race	Black	11/135	**92.6**	8/140	**93.4**	**0.70** (0.27,1.77)	0.69
	White	40/543	**91.6**	36/533	**92.1**	**1.00** (0.63,1.57)	
	Other	8/106	**91.8**	6/99	**95.3**	**0.84** (0.28,2.52)	
Tumor Subtype	Triple-negative	8/169	**95.0**	19/188	**88.4**	**2.30** (1.00,5.25)	0.037
	ER/PR+/HER2-	17/173	**90.5**	7/155	**94.0**	**0.41** (0.17,0.99)	
	ER/PR-/HER2+	20/198	**88.8**	12/183	**92.4**	**0.63** (0.31,1.28)	
	ER/PR+/HER2+	14/244	**93.3**	12/246	**95.7**	**0.99** (0.46,2.14)	
Axillary Surgery	Axil +/- SLNB	27/357	**92.0**	25/338	**91.8**	**1.02** (0.59,1.75)	0.42
	SLNB alone	32/427	**91.5**	25/434	**93.5**	**0.75** (0.44,1.26)	



Mamounas, T et al SABCS 2023 Abstract GS02-07

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Invasive Breast Cancer

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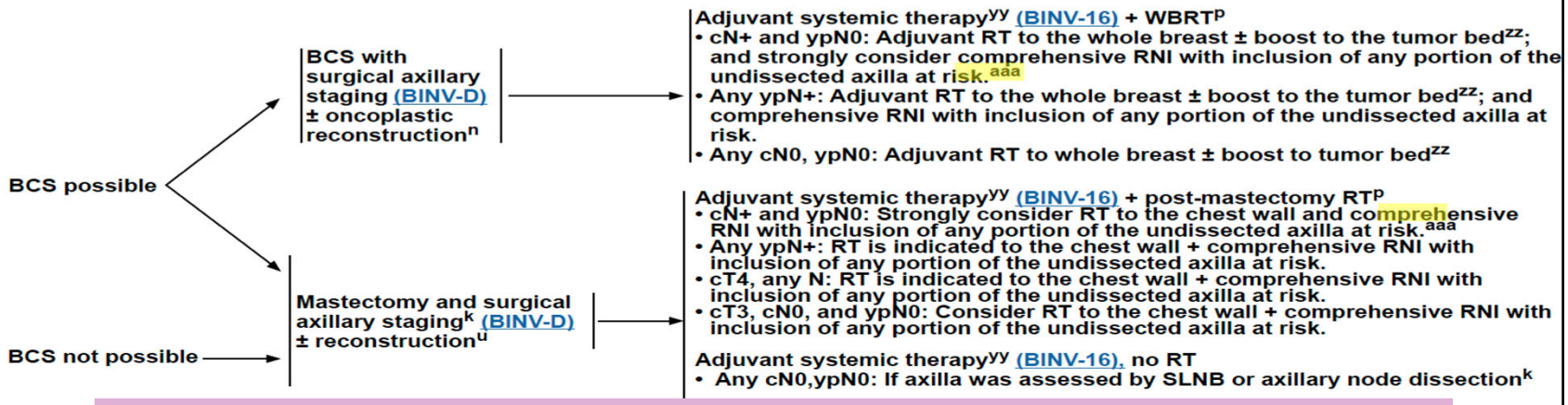
OPERABLE DISEASE: SURGICAL TREATMENT AND ADJUVANT THERAPY AFTER PREOPERATIVE SYSTEMIC TREATMENT[xx]



[n] Includes … optimizing …

[p] Principles …

[u] …

Based on emerging data, there may be subsets of patients who achieve pCR in nodes that may not benefit from RNI (in BCS setting) or PMRT + RNI (in mastectomy setting)

[aaa] Based on emerging data, there may be subsets of patients who achieve pCR in nodes that may not benefit from RNI (in BCS setting) or PMRT + RNI (in mastectomy setting). (Mamounas E, Bandos H, White J, et al. Loco-regional irradiation in patients with biopsy-proven axillary node Involvement at presentation who become pathologically node-negative after neoadjuvant chemotherapy: Primary outcomes of NRG Oncology/NSABP B-51/RTOG 1304; Abstract GS02-07; SABCS 2023.)

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Eligibility for BCT:

- *Pregnancy*
- *Multicentric Disease*

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Invasive Breast Cancer

SPECIAL CONSIDERATIONS TO BREAST-CONSERVATION THERAPY REQUIRING RT

Contraindications for breast-conservation therapy requiring RT include:

Absolute

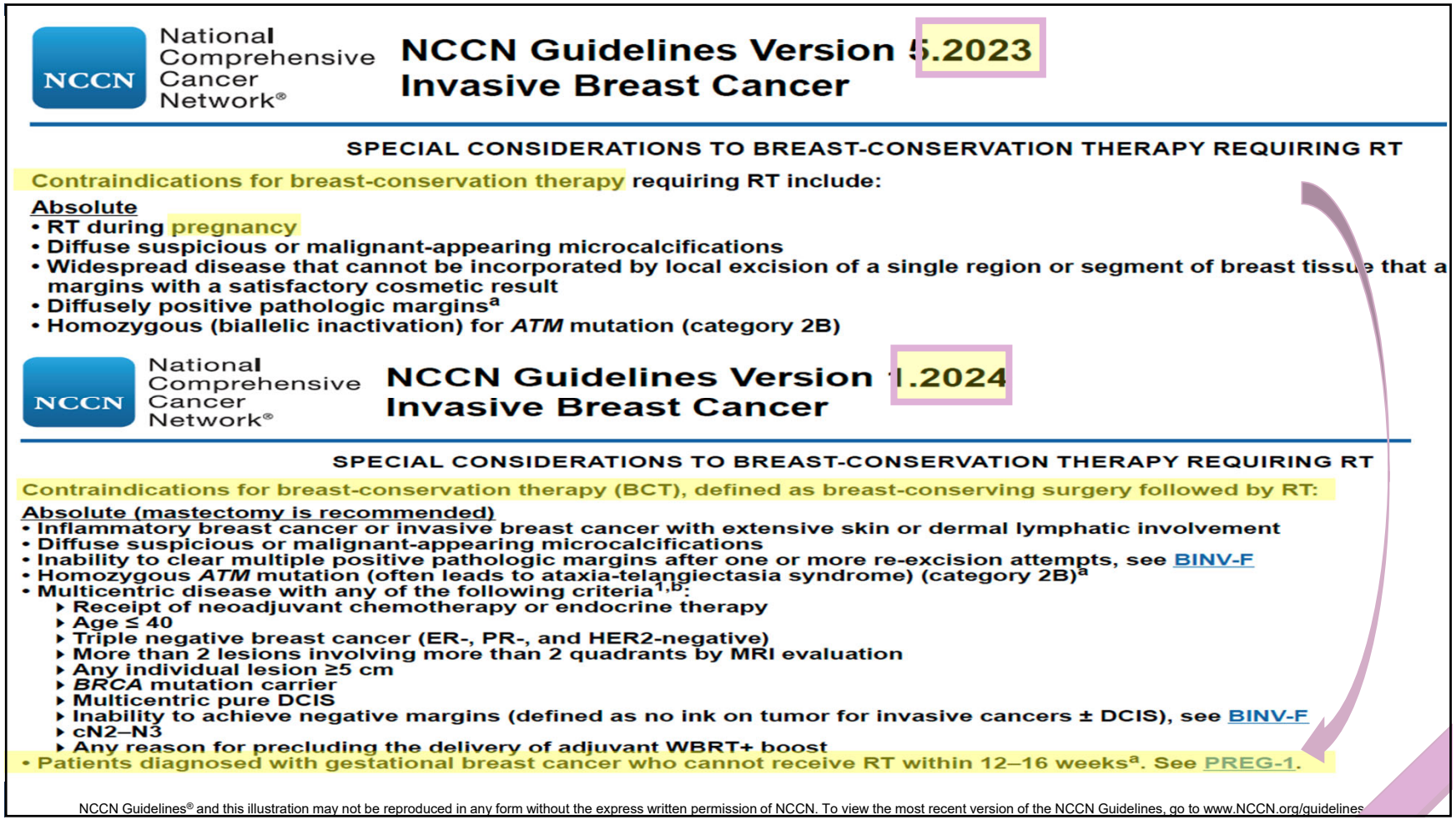
- RT during pregnancy
- Diffuse suspicious or malignant-appearing microcalcifications
- Widespread disease that cannot be incorporated by local excision of a single region or segment of breast tissue that achieves negative margins with a satisfactory cosmetic result
- Diffusely positive pathologic margins[a]
- Homozygous (biallelic inactivation) for *ATM* mutation (category 2B)

Relative

- Prior RT to the chest wall or breast; knowledge of doses and volumes prescribed is essential
- Active connective tissue disease involving the skin (especially scleroderma and lupus)
- Persistently positive pathologic margin[a]
- Patients with a known or suspected genetic predisposition to breast cancer:
  - May have an increased risk of ipsilateral breast recurrence or contralateral breast cancer with breast-conservation therapy
  - May be considered for prophylactic bilateral mastectomy for risk reduction
    (See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic)
  - May have known or suspected Li-Fraumeni syndrome (category 2B)

Pregnancy and Breast Conservation Therapy (BCT)

- BC surgery can be performed safely during all trimesters
  - BCS: Partial mastectomy/lumpectomy
  - Mastectomy
  - SLNB/ALND
- BCT (by definition) in child-bearing aged women requires RT
- Controversial whether and how much RT can be delivered during pregnancy
- RT Stochastic Effects: random mutagenic effects from RT exposure occur w/o a safe threshold
- General principle: Pregnancy-associated BC should be treated with state-of-the-art oncological treatment, while minimizing RT exposure to fetus, *without delaying treatment whenever possible*



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Invasive Breast Cancer

SPECIAL CONSIDERATIONS TO BREAST-CONSERVATION THERAPY REQUIRING RT

Contraindications for breast-conservation therapy (BCT), defined as breast-conserving surgery followed by RT:

Absolute (mastectomy is recommended)
- Inflammatory breast cancer or invasive breast cancer with extensive skin or dermal lymphatic involvement
- Diffuse suspicious or malignant-appearing microcalcifications
- Inability to clear multiple positive pathologic margins after one or more re-excision attempts, see BINV-F
- Homozygous *ATM* mutation (often leads to ataxia-telangiectasia syndrome) (category 2B)[a]
- Multicentric disease with any of the following criteria[1,b]:
  - Receipt of neoadjuvant chemotherapy or endocrine therapy
  - Age ≤ 40
  - Triple negative breast cancer (ER-, PR-, and HER2-negative)
  - More than 2 lesions involving more than 2 quadrants by MRI evaluation
  - Any individual lesion ≥5 cm
  - *BRCA* mutation carrier
  - Multicentric pure DCIS
  - Inability to achieve negative margins (defined as no ink on tumor for invasive cancers ± DCIS), see BINV-F
  - cN2–N3
  - Any reason for precluding the delivery of adjuvant WBRT+ boost
- Patients diagnosed with gestational breast cancer who cannot receive RT within 12–16 weeks[a]. See PREG-1.

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Breast Cancer During Pregnancy

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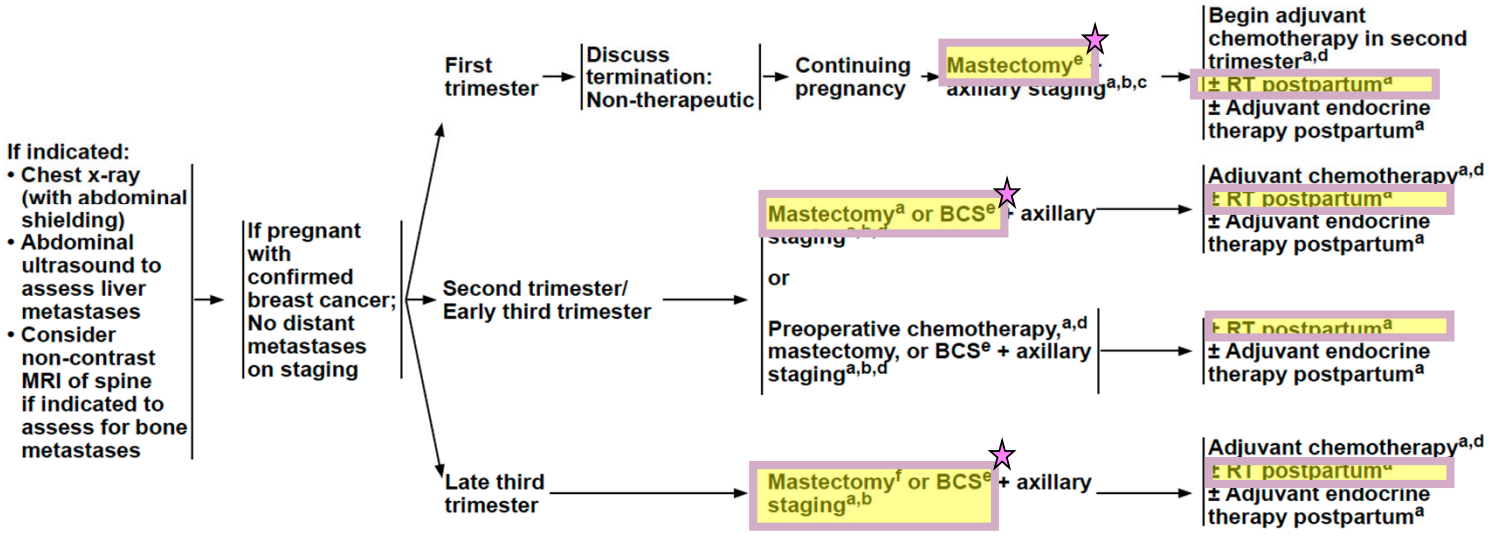

Survival outcomes of BCT are equivalent to mastectomy in both non-pregnancy and pregnancy-associated BCs. Therapeutic RT is generally avoided during pregnancy due to potential risks to the fetus. Mastectomy may be preferred, particularly for early (1st trimester) gestational diagnosis, as early BCS may preclude timely administration of RT. Generally, intervals of 12–16 weeks between treatment modalities (surgery, RT, and chemotherapy) are considered acceptable.

PREG-1. NCCN Guidelines® for Breast Cancer (Version 1.2024). © 2024 National Comprehensive Cancer Network, Inc. All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN. Available at: www.NCCN.org/guidelines.

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Invasive Breast Cancer

SPECIAL CONSIDERATIONS TO BREAST-CONSERVATION THERAPY REQUIRING RT

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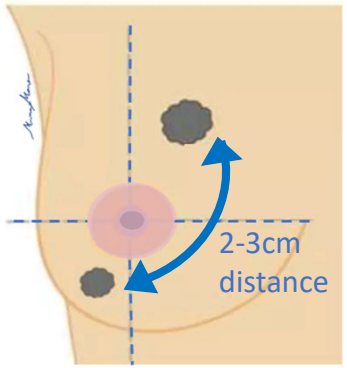
  - May be considered for prophylactic bilateral mastectomy for risk reduction
    (See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic)
  - May have known or suspected Li-Fraumeni syndrome (category 2B)

Multicentric BC and Eligibility for BCT: Alliance 11102

- Single arm prospective trial N=204



Eligibility criteria:

- >40 years
- MRI-proven 2 (or 3) lesions
- 2-3 cm of normal tissue bt tumors
- Only 2 quadrants involved
- <5 cm tumors
- At least one invasive ca
- cN0 or cN1

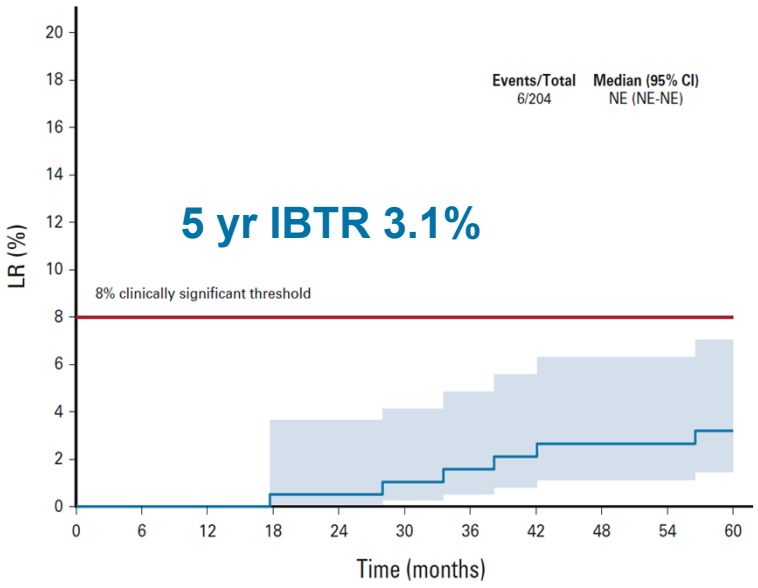
Exclusion criteria:

- BRCA mutation carriers
- Pts w/breast implants
- Pts receiving NAT
- Anyone for whom WBRT + boost was contra-indicated
- Inability to achieve negative margins

- Protocol required WBRT +Boosts +/-RNI
- Tumor bed boosts were mandated to each site of disease
- Doses: 45-50 Gy/1.8-2.0 Gy WBRT + 10-16 Gy to tumor beds

Boughey J et al, JCO 2023

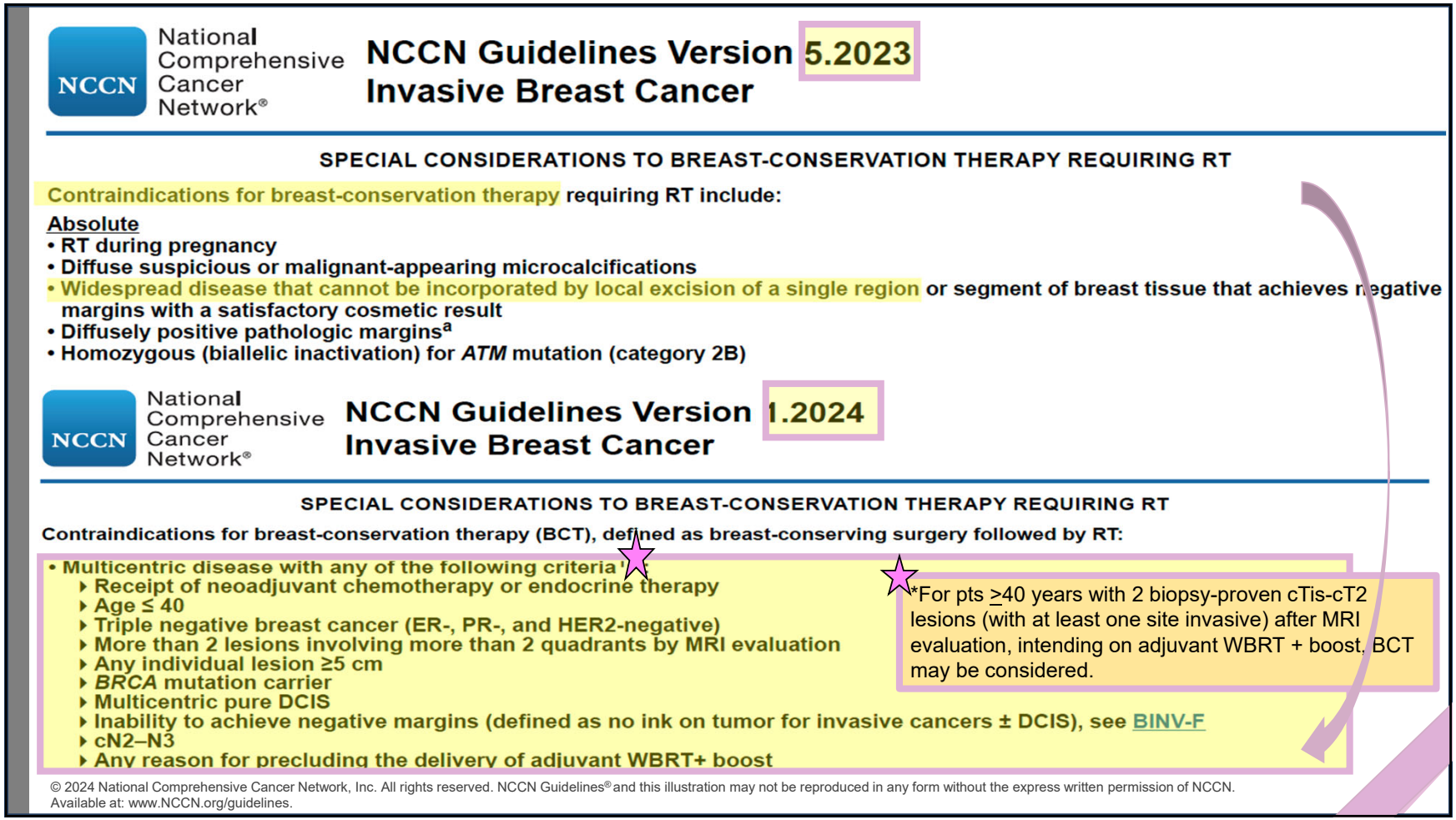
Alliance 11102 Results



Boughey J et al, JCO 2023

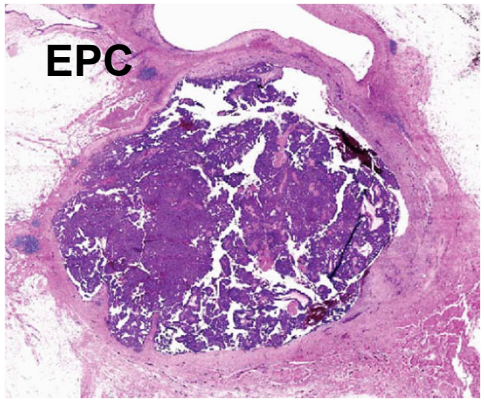
Important Patient Characteristics:

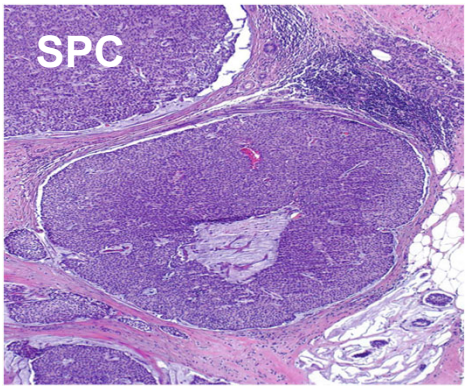
- Median age 62 yrs; Median f/u 66 mo
- MRI: 93%
- MRI (additional malignant lesion): 42%
- 5-year LR rate w/MRI vs. w/o MRI:
  - MRI:1.7% vs. ⌀MRI: 22.6%
  - HR: 13.49 (95%CI,2.72-66.90) p=0.002
- 2 vs. 3 lesions: ~96% vs. 4%
- Tumor Biology:
  - ER+/HER2-: ~83%
  - HER2+(any ER): ~12%
  - ER-/HER2-: 5%



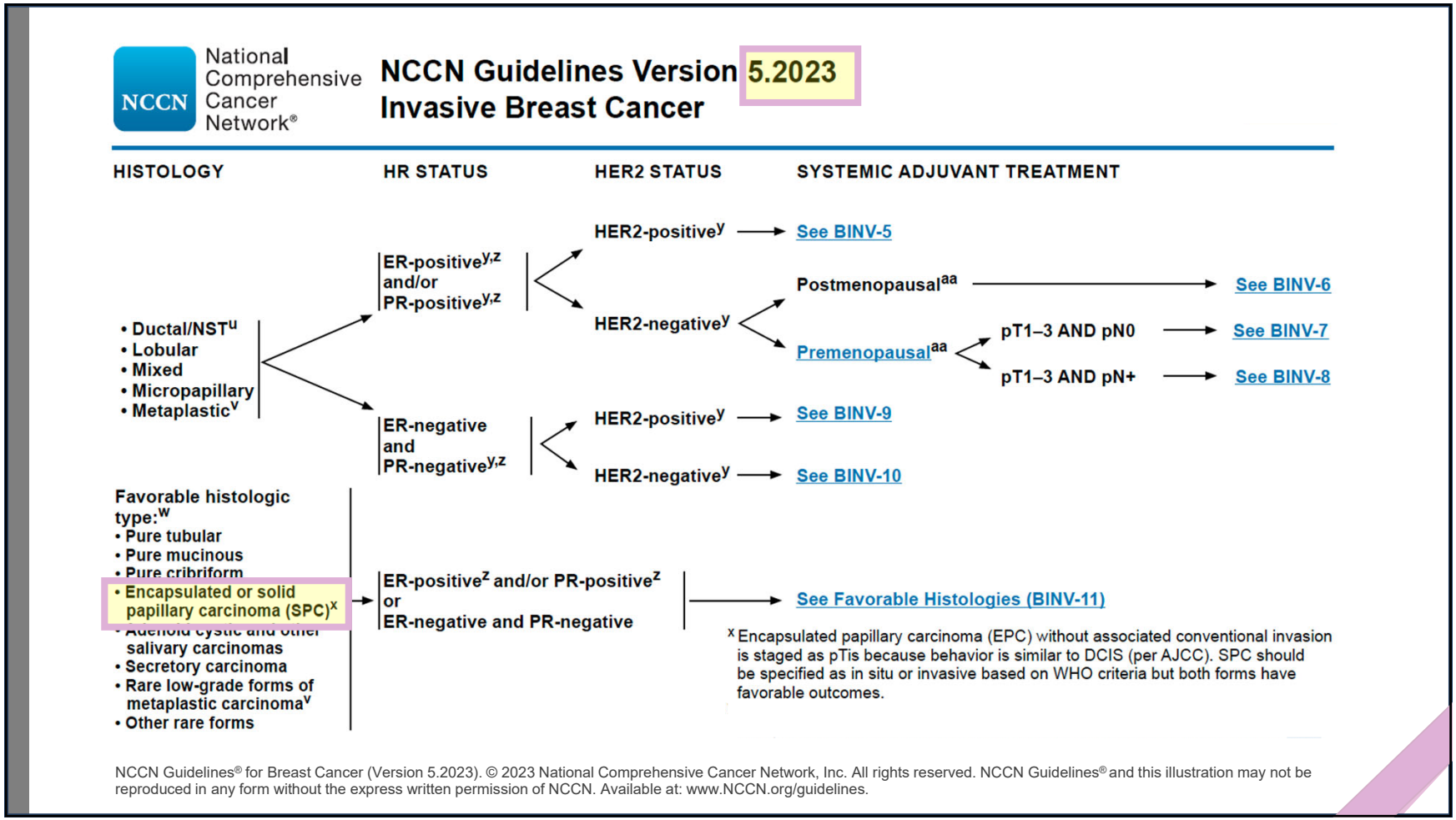
DCIS 1

Encapsulated Papillary/Solid Papillary Carcinoma (EPC/SPC)

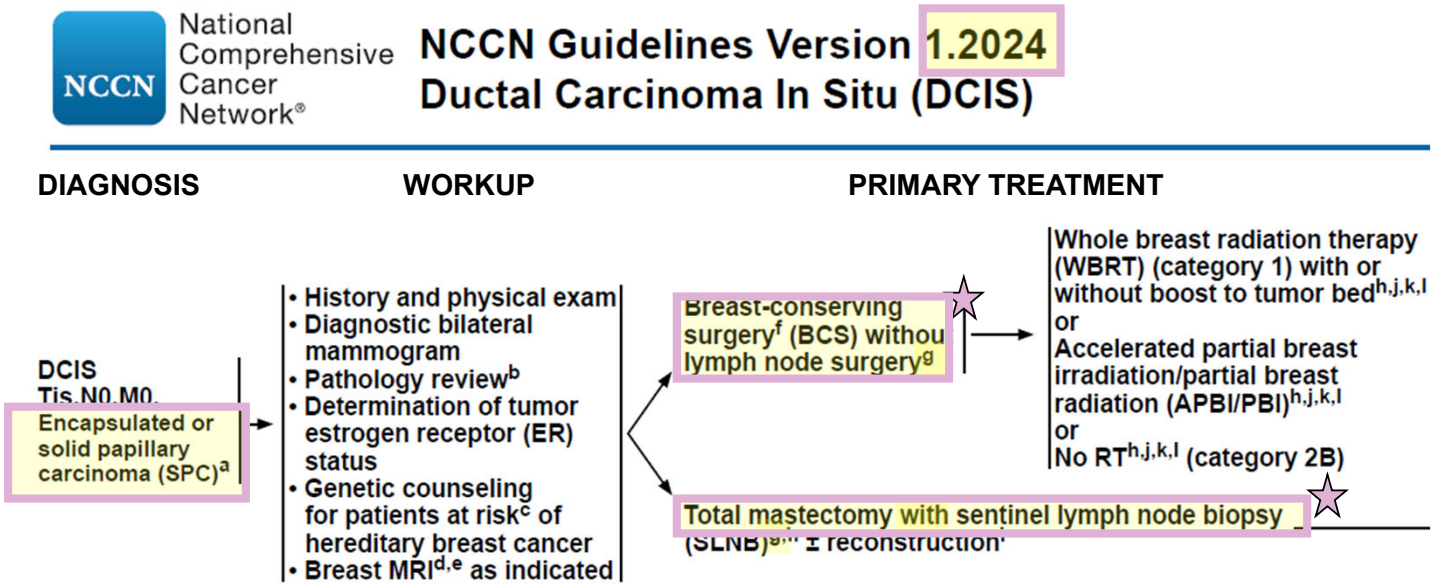




EPC	SPC
Well-defined capsule surrounding the tumor	Solid papillary growth pattern without capsule
Primarily intraductal (can be invasive)	Primarily intraductal, can have invasive foci



Ductal Carcinoma *In-situ*



National Comprehensive Cancer Network®

NCCN Member Institutions

Who We Are

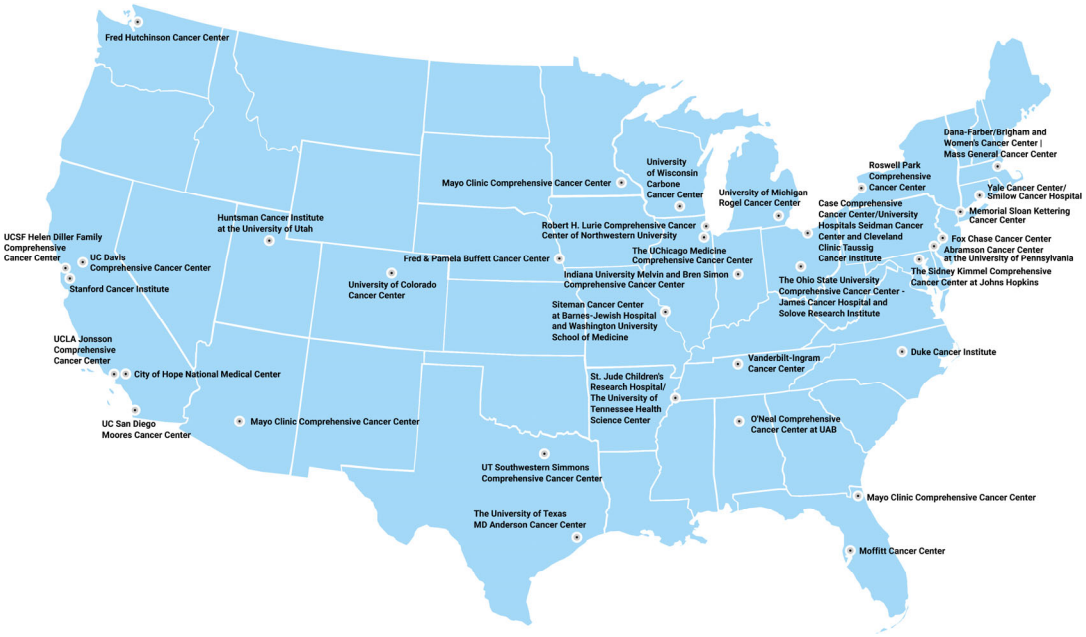
An alliance of leading cancer centers devoted to patient care, research, and education

Our Mission

To improve and facilitate quality, effective, equitable, and accessible cancer care so all patients can live better lives

Our Vision

To define and advance high-quality, high-value, patient-centered cancer care globally



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